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OBSERVATIONS ON THE VARIABILITY OF TOTAL SERUM CHOLESTEROL IN JOHNS HOPKINS MEDICAL STUDENTS

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AS PART of a broad investigation of possible precursors of hypertension and coronary artery disease, the total cholesterol levels in blood serum have been determined on one or more occasions in successive classes of Johns Hopkins medical students. The long-term objective of these observations is to ascertain whether or not the cholesterol level in early adult life is of predictive value in regard to the future appearance of such cardiovascular disease.[1] The purpose of the present paper is to establish the norms for our group of subjects by statistical methods and to make relevant comparisons, wherever possible, with other data in the literature.

During the past thirty-five years, many investigators have contributed to the understanding of the significance of the serum cholesterol level in a given individual. A wide variety of excellent papers dealing with this subject has been published, and it is not our intent to make a detailed analysis of the literature here. Some of the current concepts which are pertinent to the present studies may be summarized as follows:

1. The total serum cholesterol of healthy adults has a wide range of normal values.[2-8]

2. The exact numerical value of cholesterol is a function of the particular laboratory technique employed and should be judged in that framework.[9-11]

3. There is very little or no difference in the cholesterol level after eating as compared with that in the fasting state.[3,12-16]

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4. As age advances, the level of cholesterol rises gradually until middle life in healthy men as a group but does not increase until after middle life in healthy women.[2,17-22]

5. Despite measurable fluctuations, there is relative constancy of cholesterol levels over periods of weeks or months in a normal individual.[4,5,20,23-27]

6. Total cholesterol levels in patients with coronary artery disease tend to be more inconstant and to fluctuate more widely than those in a normal control group.[25,26,28]

7. On the average, patients with coronary artery disease have higher cholesterol levels than do normal subjects.[25,26,28-35]

8. There are individuals in apparent good health with excessively high cholesterol levels or hypercholesteremia.[2,19,36]

9. There is more coronary artery disease in the families of subjects with hypercholesteremia than in families of subjects without that trait.[37-44]

In the present analysis of data from healthy young adults, comparisons with the work of others will be made in the body of the paper, particularly in regard to the fourth and fifth concepts previously stated. The concepts concerning hypercholesteremia have been the subject of a recent paper based on the same population of medical students.[45] The other concepts will be dealt with in later studies.

GENERAL PROCEDURE

Cholesterol determinations were obtained on a voluntary basis from 759 Johns Hopkins medical students, both men and women, between October, 1948, and June, 1956. The general statistical analyses of technical error, relationship of age, sex, and time lapse to cholesterol level and total variability were carried out on groups drawn from the 612 subjects in the first 10 classes (1948-1957) who had had one or more determinations before June 1, 1955. Additional data obtained from 147 subjects in the classes of 1958 and 1959 have been included in a few sections. Many of the latter determinations as well as some repeated after 4 to 8 years on a small number of the original 612 subjects were made in the year 1955-1956. Beginning in 1948, with the class of 1952, determinations were made systematically on the entering students. Repeat tests and tests on subjects already in medical school when the cholesterol program was started were obtained as the subjects came to the project laboratory for other purposes.

The students were in that state of health and activity consistent with the pursuit of their medical studies. None had overt coronary artery disease, hypertension, or any of the disorders usually associated with altered cholesterol metabolism, except for several individuals in compensated states of health who are listed later in Table V. Blood was drawn during the academic day with the subjects in the nonfasting state (most often between two and four in the afternoon). No attempt was made to alter the subjects' diets.

Chemical Method.—The modified Bloor method described below was used throughout. All cholesterol determinations were carried out in the Clinical Chemistry Laboratory of the Johns Hopkins Hospital under the direction of Dr. Frederick W. Barnes, Jr., and the supervision of Mrs. Florence B. White. The technique employed was an adaptation of the Sackett[46] modification of the Bloor method

made a number of years ago by Dr. Mary V. Buell. To meet the laboratory's demands of accuracy and reproducibility, rigorous control was instituted in regard to the factors of time, temperature, mixing, and, most importantly, light as they affect the development of the color reaction. The procedure of extracting cholesterol from the serum was also standardized. Because the results are so reproducible, the details of the technique as used daily in the Johns Hopkins Hospital are published here for the first time with Dr. Buell's permission.

Cholesterol in Serum

Principle.—The proteins are precipitated and the sterols extracted in one operation with hot alcohol-ether. This solvent is subsequently evaporated and replaced by chloroform. The Lieberman-Burchard reaction is developed in the chloroform solution, the green color being measured with light of wave length 625 mμ.

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Reagents.—

1. Solvent.
   Make a 3 to 1 mixture of 95 per cent alcohol and C.P. ethyl ether (300 c.c. of alcohol plus 100 c.c. of ether). Protect against moisture.
2. Chloroform (U.S.P. or C.P.).
3. Acetic anhydride.
4. Concentrated sulfuric acid.
5. Cholesterol reagent (prepare just before use). Introduce into an Erlenmeyer flask 4 c.c. of acetic anhydride for each determination (+2 c.c. extra). Holding the flask in an ice water bath, add *slowly* exactly 0.1 c.c. of H_2SO_4 for each 1 c.c. of acetic anhydride. This reagent should be used within one hour after preparation.

Procedure.—Introduce about 17 c.c. of solvent into a 25 c.c. volumetric flask. Add exactly 1 c.c. of serum while rotating the flask. Bring the contents of the flask to the boiling point in a hot water bath. Remove the flask from the water bath for a moment. Reheat until the contents boil. Remove the flask and reheat a second and a third time to boiling. Cool under running cold water. Make to volume with the solvent. Filter and stopper the bottle containing the filtrate. Pipette 5 c.c. of the filtrate into a dry Pyrex test tube. Add a Hengar crystal. Introduce about 300 c.c. of hot water into a 600 c.c. beaker. Place the beaker on a hot plate under the hood. Keep the temperature of the water near the boiling point. Evaporate the solvent by placing the test tube in the hot water until the volume remaining in the tube is less than 0.5 c.c. (Do not evaporate to dryness.) Add about 1 c.c. of chloroform and evaporate once more in the water bath until the residue just appears to be dry. Cool the tube spontaneously. (If chloroform vapors condense, evaporate once more.) Add exactly 10 c.c. of chloroform. Stopper the tube loosely and set it in a water bath at 25° C. for 5 minutes. Meanwhile, prepare the cholesterol reagent. Add exactly 4 c.c. of reagent to each tube at intervals of 1 minute. Stopper each tube with a glass stopper and mix well. Allow each tube to stand in the dark for exactly 10 minutes at 25° C. before reading the color. Read each tube in the photoelectric colorimeter, with the light of wave length 625mμ, using chloroform as a reference (blank) solution. Determine the concentration of cholesterol in milligrams per 100 c.c. of serum from the appropriate curve, in which each point is determined as described below.

Preparation of Standard Cholesterol.—Recrystallize Merck's U.S.P. cholesterol from absolute alcohol twice. Dry over phosphorus pentoxide at 105° C. until it has reached constant weight.

Standard Solutions.—

Stock Standard. (5 c.c. = 8.0 mg. cholesterol.)
Dissolve 400 mg. of pure cholesterol in 250 c.c. of chloroform in a 250 c.c. volumetric flask. Transfer to a reagent bottle. Seal with paraffin and store in refrigerator.

Working Standard. (5 c.c. = 0.4 mg. cholesterol.)
Dilute 5 c.c. of stock standard to 100 c.c. with chloroform in a 100 c.c. volumetric flask. Transfer to a reagent bottle. Seal with paraffin and store in refrigerator.

To prepare calibration curve for Coleman Spectrophotometer use the following dilutions of standard in 20 by 150 mm. test tubes:

c.c. working standard	c.c. chloroform	equivalent mg. per cent cholesterol
2	8	80
5	5	200
7	3	280
10	0	400

Stopper loosely and place in a 25° C. water bath. Proceed as for unknowns. Read per cent transmission at wave length 625 mμ. and plot on semilog paper.

It is estimated from collected results of the Johns Hopkins Hospital Chemistry Laboratory that about 90 per cent of normal individuals will show values between 150 and 275 mg. per 100 c.c. of serum cholesterol.

Reliability of Method.—In order to test the technical accuracy of the modified Bloor method as it is performed in the Johns Hopkins Laboratory, duplicate tests were run on 78 individuals from the classes of 1955, 1957, and 1958 during the spring of 1955. Two blood samples from the same venepuncture were labeled with different names and sent to the Chemistry Laboratory together with other samples. Precautions were taken so that it would not be possible for the laboratory technicians to identify such duplicate determinations. Twenty-eight pairs of determinations showed exact agreement, while in an additional 44 pairs, the absolute difference between pairs lay between 1 and 25 mg. per 100 c.c. inclusive. The remaining 6 pairs were less consistent; 2 of these were discarded because of extreme variation and the probability of calculation error in the laboratory. Thus 94.7 per cent of a series of 76 duplicate tests were consistent, while only 4 pairs, or 5.3 per cent, showed absolute differences greater than 25 mg. per 100 c.c. (Table XVIII).

In the spring of 1956, a second series of duplicate cholesterol determinations was run in similar fashion on 72 subjects from the class of 1959. The product-moment correlation coefficient "r" was found to be high ($r = 0.93$), and almost identical to that for the series of the previous year after the 2 discordant pairs of observations were removed (Table I). Accordingly, it would seem that $r = 0.92$ is a measure of the degree of technical reproducibility of the modified Bloor method itself as performed in the Johns Hopkins Hospital Laboratory. This is very close to the value obtained by the Gofman group using the Schoenheimer-Sperry method based on data from 532 duplicate tests.[47] However, it is a smaller value than $r = 0.98$ obtained by Man and Gildea[5] twenty years ago on 100 consecutive determinations by the method of Man and Peters.

As another measure of duplicate reproducibility, the technical error of measurement in milligrams per 100 c.c. (s_e) was also estimated for our two successive series of duplicate determinations (Table II). The s_e for both series lay near 11 mg. per 100 c.c. This indicates that a single observation would be expected to differ from its true value by more than $\pm$ 11 mg. per 100 c.c. in less than one-third of the trials due to the effects of technical error of measurement alone. The re-

TABLE I. CORRELATION COEFFICIENTS FOR DUPLICATE CHOLESTEROL DETERMINATIONS ON SAME SERUM SAMPLE

DATA	CHEMICAL METHOD	N	CORRELATION COEFFICIENT $r \pm s_r$
Johns Hopkins	Bloor		
Series 1955		76*	0.92 ± 0.02
Series 1956		72	0.93 ± 0.02
Total		148*	0.92 ± 0.01
Gofman et al.†[47]	Schoenheimer-Sperry	532	0.91 ± 0.01†
Man and Gildea[5]	Man and Peters	100	0.98 ± 0.005‡

*Omitting two outlying pairs of determinations; see text.

†Correspondence with Dr. Gofman indicates that 0.91 ± 0.01 is the correct value.

‡s_r was computed by us.

TABLE II. ESTIMATES OF THE TECHNICAL ERROR OF MEASUREMENT (s_e) FOR DUPLICATE DETERMINATIONS FROM DIFFERENT INVESTIGATORS

DATA	METHOD	NUMBER OF PAIRS OF DUPLICATE TESTS	s_e*
John Hopkins	Bloor		
Series 1955		76	11.2
Series 1956		72	10.1
Chandler, Lawry, Potee, and Mann[27]	Abell	98	14.5
Cooperative Study of Lipoproteins and Atherosclerosis†[8]			
Cleveland Clinic (Page)	Abell	514	7.6
Harvard (Stare and Mann)	Abell	512	10.5
Donner Laboratory (Gofman)	Coleman	194	17.3

*The technical error of measurement is:

$$s_e = \sqrt{\frac{\epsilon\, d^2}{2k}}$$

in which d = difference between duplicate determinations and k = number of pairs.

†The Pittsburgh data are omitted because of the small number of duplicate tests reported.

producibility of a cholesterol determination by the Bloor method as performed in the Johns Hopkins Hospital Chemistry Laboratory compares favorably with similar duplicate tests carried out in four different laboratories using two other methods. Only the data obtained by the Cleveland Clinic group using the method of Abell, Levy, Brodie, and Kendall appeared to be superior to the Johns Hopkins data in terms of reproducibility. However, it is to be noted that neither the data of Chandler and his associates nor that of the Harvard group were more reproducible than the Johns Hopkins data although they were based on the same method as that used by the Cleveland group.

It was observed by Chandler's group concerning total cholesterol that "the error of measurement increases with increases in the concentration being measured."[27] The later studies of Watkin, Lawry, Mann, and Halperin[20] using the method of Abell also indicate that there is a rise in technical error with rise in mean cholesterol level, and they further found that the standard error among duplicate tests increases about 0.08 mg. per 100 c.c. for each milligram per 100 c.c. increment in total cholesterol. Our duplicate test studies were examined from this point of view for first cholesterol values of 150 to 299 mg. per 100 c.c. Both series suggest that technical error of measurement may be higher for cholesterol determinations between 250 to 299 mg. per cent than for lower values (Table III). However, the sample sizes at this level are quite small. When our two series were combined, we found that the technical error of measurement for levels 150-199, 200-249, and 250-299 mg. per 100 c.c. was 6.4, 10.1, and 14.0 mg. per 100 c.c., respectively. There was roughly a 4 mg. per 100 c.c. increase in the technical error for each 50 mg. per 100 c.c. increase in cholesterol level, which comes out to 0.08 mg. per 100 c.c. for each milligram per 100 c.c. increment in total cholesterol, the same figure as was cited previously from the extensive Watkin studies.

TABLE III. AGREEMENT OF DUPLICATE TESTS FROM SAME SERUM SAMPLE AT THREE DIFFERENT CHOLESTEROL LEVELS

SERIES	FIRST CHOLESTEROL LEVEL* BETWEEN	NUMBER OF INDIVIDUALS	TECHNICAL ERROR OF MEASUREMENT (s_e)	PERCENTAGE OF INDIVIDUALS AT EACH LEVEL SHOWING DIFFERENCES BETWEEN DUPLICATE TESTS OF		
				0 TO ± 9 MG. %	± 10 TO ± 19 MG. %	± 20 MG. % OR MORE
	MG. %		MG. %	%	%	%
1955	(1) 150-199	21	6.3	66.7	33.3	0
	(2) 200-249	39	12.2	77.0	15.4	7.7
	(3) 250-299	13	14.1	38.5	46.2	15.4
1956	(1) 150-199	21	6.6	66.7	28.6	4.8
	(2) 200-249	32	6.7	78.2	15.6	6.2
	(3) 250-299	16	13.9	68.8	6.2	25.0
Total	(1) 150-199	42	6.4	66.7	31.0	2.4
	(2) 200-249	71	10.1	77.5	15.5	7.0
	(3) 250-299	29	14.0	55.2	24.1	20.7
	(1)-(3) 150-299	142	10.2	69.7	21.8	8.5
All Data	100-399	148	10.7	68.9	21.6	9.5

*Which one of the duplicate tests was "first" was determined entirely by chance.

A look at the percentage of duplicate tests at each cholesterol level with differences between the two tests of 0 through ±9, ±10 through ±19, and ±20 mg. or more per 100 c.c. also suggests that large differences are relatively more frequent at the 250-299 mg. per cent level. There were only 4 individuals in the duplicate test studies with first cholesterol determinations of 300 mg. per 100 c.c. and over, so that what happens to the technical error at hypercholes-

teremic levels cannot be estimated statistically from our material. The 4 pairs of tests from the same serum samples and their differences were as follows:

Cholesterol: (in mg. per 100 c.c.)	325, 317 (−8);	308, 317 (+9);	335, 345 (+10);	317, 258 (−59)
Subjects:	58134	59153	59125	59155

The differences in these tests resemble those found for the total 29 subjects with first cholesterol levels of 250-299 mg. per 100 c.c. (Table III)

RESULTS

A. *Over-all Findings on Total Population of Subjects.*—The frequency and percentage distribution of the first cholesterol determinations among the 612 medical students, both men and women of all ages, is given in Table IV. The mean value for the entire group was 228.7 mg. per 100 c.c. with a standard deviation of 43.3 mg. per 100 c.c., while the range lay between 108 and 407 mg. per 100 c.c. The modal class value lay between 200 and 224 mg. per 100 c.c., decreasing more gradually in the direction of higher than of lower values, so that the curve is somewhat skewed. When cholesterol levels are grouped by class values of 50 mg. per 100 c.c., as in Fig. 1, the skewness of the curve appears as a slight prominence only.

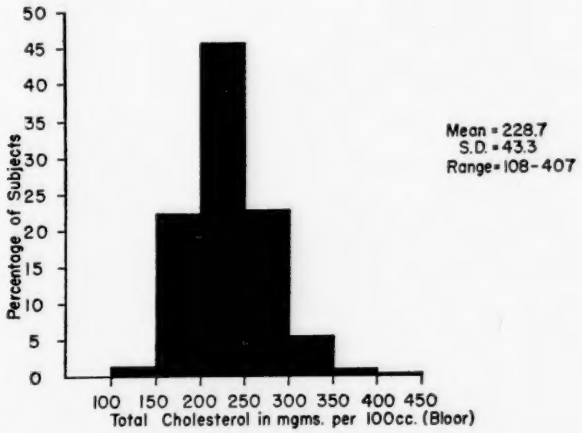

Fig. 1.—Frequency distribution of blood cholesterol levels among 612 medical students.

Although by the Bloor method, 275 mg. per 100 c.c. is often considered to be the upper limit of the normal range, approximately one medical student in 8 had cholesterol levels exceeding this value. Definite hypercholesteremia at levels of from 300 through 407 mg. per 100 c.c. at first test occurred in 6.4 per cent of the population. Nothing unusual was found in regard to the health of the hypercholesteremic subjects themselves, but a history of coronary artery disease affecting the fathers of these students occurred with unwarranted frequency.[45] It was found that 32.1 per cent of the 53 hypercholesteremic*

*As determined *either* at first *or* at subsequent test.

subjects had a parent affected by coronary disease in contrast to 11.8 per cent of the subjects with cholesterol values below 300 mg. per 100 c.c. This difference was highly significant (P = <0.001).

TABLE IV. FREQUENCY AND PERCENTAGE DISTRIBUTION OF FIRST CHOLESTEROL DETERMINATIONS IN A POPULATION OF 612 MEDICAL STUDENTS

SUBJECTS	TOTAL SERUM CHOLESTEROL IN MG. PER 100 C.C. (BLOOR METHOD)												
	100-124	125-149	150-174	175-199	200-224	225-249	250-274	275-299	300-324	325-349	350-374	375-399	400-424
No.	3	5	45	98	170	108	104	40	24	7	3	4	1
%	0.5	0.8	7.4	16.0	27.8	17.6	17.0	6.5	3.9	1.1	0.5	0.7	0.2
%	1.3				92.3				6.4				

Range: 108 to 407 mg. per 100 c.c.
Mean: 228.7 mg. per 100 c.c. ± 43.3

TABLE V. HEALTH EXCEPTIONS

SUBJECT NO.	FIRST CHOLESTEROL DETERMINATION IN MG. PER 100 C.C.	HEALTH CONDITION
51103*	108	Quiescent regional ileitis
49131*	122	Taking thyroid extract 1 grain daily for low BMR without true hypothyroidism
50138*	118	Diabetes mellitus under good insulin control
52128	245	Same
53120	195	Same
55154	177	Same
49222*	214	Postthyroidectomy hypothyroidism corrected by thyroid extract. BMR normal

*See Table XVI.

In contrast to the frequency of hypercholesteremia, subjects were seldom encountered with cholesterol levels below 150 mg. per 100 c.c., which is often thought of as the lower limit of the normal range by this method. Moreover, the three subjects with the lowest values at first test (below 125 mg. per 100 c.c.) had conditions which might have modified their cholesterol levels* (Subjects 51103, 50138, and 49131, Table V). It would therefore appear that such normal young adults rarely have such low values.

*Among the 612 "normal" young adults, a variety of health problems existed, yet all were healthy in the sense of being fit to pursue their work actively. In order to learn as much as possible about the entire group and to avoid introducing bias, no subjects were excluded from the analysis. In retrospect, 7 subjects might have been excluded for the reasons shown in Table V. With the exception of slightly altering the range of values at its lower limit, it is not thought that inclusion of these data on about 1 per cent of the entire group studied has affected the general findings.

Although the range of normal cholesterol levels among these subjects seems wide, it is not so great when compared with the entire range of human cholesterol values, the extremes of which are encountered only in certain disease states. In the Johns Hopkins Hospital Chemistry Laboratory, cholesterol determinations as low as 60 mg. per 100 c.c. and as high as 2,500 mg. per 100 c.c. are observed occasionally during the course of a year among a population of patients of all ages.

The findings for each of the successive classes of students are summarized in Table VI. In general, the cholesterol values are compatible. There is no consistent trend either in the means or in the lower or upper limits of the range to indicate that the laboratory technique or the composition of the student body has changed markedly over the years.

B. *Relationship of Age and Sex to Cholesterol Level.*—Of the total 612 subjects, 562 were men, and only 50 were women. Table VII gives a summary of the cholesterol levels of the women as a group compared with the men. At similar mean ages of about 23 years, there is no real difference in the average cholesterol level (230.6 mg. per 100 c.c. for women versus 228.5 for men).

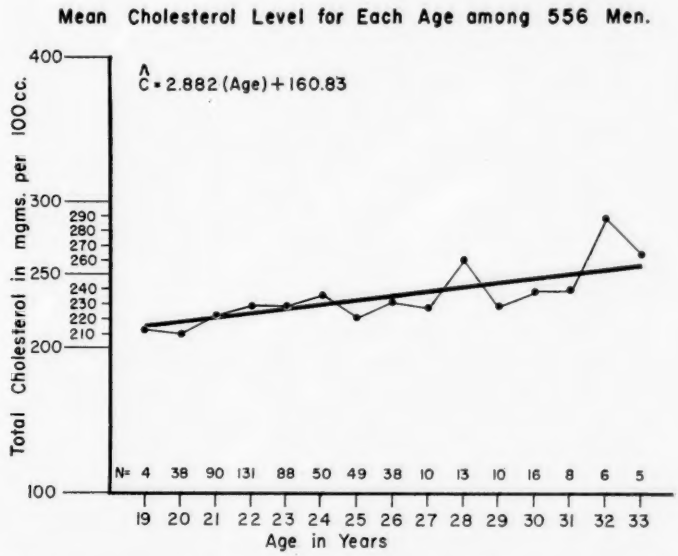

Fig. 2.—Mean cholesterol level for each age among 556 men. (From Thomas, C. B.: Am. J. M. Sc. **232**:389, 1956. By permission of Lea & Febiger.)

The relationship of age to cholesterol level was first analyzed in detail among the men. Only that range of ages was considered where there were four or more subjects at each age at first test. Six men aged 34 to 49 years were thus eliminated, leaving 556 men between the ages of 19 and 33 inclusive. A plot of the mean total cholesterol at each age shows a rise in cholesterol level with age (Fig. 2). This rise is significant and was demonstrated in several ways:

1. A straight line equation was derived: $\hat{C} = 2.882\ (\text{Age}) + 160.83$, where $\hat{C}$ is the expected mean cholesterol. The slope of 2.882 ($s_b = 0.623$)

TABLE VI. TOTAL SERUM CHOLESTEROL LEVELS OF SUCCESSIVE CLASSES OF MEDICAL STUDENTS

GROUP	CLASS: YEAR OF GRADUATION	NO. OF SUBJECTS TESTED	FIRST CHOLESTEROL DETERMINATIONS IN MG. %		AGE AT TEST IN YEARS	
			MEAN	RANGE	MEAN	RANGE
A	1948	5	223.0	168 316	24.6	20–30
	1949	32	216.6	122 308	25.0	20–34
	1950	59	245.7	118 407	27.3	21–37
	1951	67	226.0	108 333	25.6	20–33
B	1952	77	223.1	160 320	23.0	19–49
	1953	77	237.5	128 378	22.9	20–35
	1954	75	238.5	150 355	22.9	19–29
	1955	77	215.7	150 298	22.4	19–28
	1956	69	223.1	150 335	22.6	20–30
	1957	74	228.4	150 375	22.2	19–29
C	1958	75	229.9	150 386	22.4	19–34
	1959	72	212.6	140 298	21.9	19–28

Groups A and B comprise the original 612 subjects; those in Group C were added later. In Groups B and C initial cholesterol levels were obtained during the first year in medical school, while in Group A they were obtained for the first time later in the academic course. Almost all subjects in the classes of 1952 through 1959 had cholesterol determinations.

TABLE VII. COMPARISON OF CHOLESTEROL LEVELS IN MEN AND WOMEN

	MEN	WOMEN	MEN AND WOMEN
Number of subjects	562	50	612
Mean cholesterol level (in mg. per 100 c.c.)	228.5	230.6	228.7
Standard deviation	42.7	49.7	43.3
Range of cholesterol levels	108–390	125–407	108–407
Mean age	23.6	22.9	23.6
Age range	19–49*	19–29	19–49*

*All but six were below the age of 34 years.

is significantly different from zero ($P<0.001$) and has 95 per cent confidence limits of 1.655 and 4.109. This means that there is approximately a 3 mg. per 100 c.c. rise in mean cholesterol for each year's rise in age over the range of 19 to 33 inclusive, with an average total rise of 42 mg. per 100 c.c. over the 14-year span. Our slope of 2.882 ± 0.623 is in statistical agreement with Keys' data on Minnesota men (chiefly students) between 17 and 45 inclusive and of similar age distribution Table VIII).[18] In his series, 22 per cent of the subjects were over 25, compared with 19 per cent in our series. The average age for both series is about the same. Recently Adlersberg, working with healthy industrial workers in Staten Island, N. Y., showed that "from ages 20 through 33 there was a significant increase of total cholesterol level, averaging 3.6 mg. per 100 c.c. per year" for men.[22] Again, our slope is in statistical agreement with his result (Table VIII).

TABLE VIII. ESTIMATES OF THE AVERAGE RISE IN MEN PER YEAR OF AGE OF TOTAL SERUM CHOLESTEROL (b) IN MG. PER 100 C.C.

AUTHORS	LABORATORY METHOD	AGE		NO. OF MEN	CHOLESTEROL IN MG. %			
		RANGE	MEAN		MEAN LEVEL	b	s_b	P*
Johns Hopkins data	Bloor	19–33	23.48	556	228.5	2.882	± .623	< .001
Keys et al.[18]	Schoenheimer-Sperry and Bloor	17–45	23.65	1172	181.9	2.29	± .18	
Adlersberg et al.[22]	Schoenheimer-Sperry	20–33	—	74	226.1†	3.622		0.01 > P > 0.001

*Probability of obtaining a slope so large if the true value were zero.
†From correspondence with Adlersberg.

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2. The data were combined into age groups in order to build up large enough numbers and "t" tests were run to see at what points the change in mean cholesterol level with chronologic age was statistically significant. The initial computations are presented in Table IX. Table X shows that each of the following age groups is distinct from one or two of the others: 19-20, 21, 22-27, 28-33. The corresponding mean cholesterols are approximately 210, 220, 229, and 250 mg. per 100 c.c. The 19-20 year olds are significantly different from the 22-27 and 28-33 year olds; the 21 year olds are significantly different from the 28-33 year olds; the 22-27 year olds are significantly different from the 19-20 and 28-33 year olds. The age of 21 with a large series of 90 men was not combined; it appears as a transition age. It is interesting that Keys speaks of 25 to 32 as ages "where the progression of cholesterol with age seems to have halted for a few years."[18] A similar phenomenon appears among the Johns Hopkins men in the 22-27 year period, occurring when they are somewhat younger and for a shorter time span than the pause noted by Keys. Accordingly, it may be argued that it is more valid to consider the effect of age on the average cholesterol level in terms of the age groups established in Table X, rather than in terms of a uniform linear regression.

3. As was pointed out in a previous paper, "The rise in mean cholesterol associated with age appears to come from altered proportions of those with high and low values, rather than from an aging effect in all individuals."[45] Table XI shows the per cent of men at a given age with first cholesterol levels < 200, 200-249, and $\leqq 250$. For the total group of 556 men, the per cent of those with first levels below 200 and those of 250 or above is about equal, i. e., 24 per cent and 29 per cent, respectively. Forty-seven per cent of the total group have levels between 200 and 249. A breakdown by age shows that:

a. Fourteen per cent of the men 28 to 33 years of age have levels under 200, while nearly three times as many men 20 years or less have these low levels.
b. More than half of the men aged 28 to 33 have levels of 250 or more, while 12 per cent of the men 19 and 20 years of age have such levels.

When a straight line equation and "t" tests were considered for the cholesterol data at the first test for men at ages 19-33 inclusive, two questions were examined: first, whether the cholesterol values were normally distributed about the mean of the series for a given age, and second, whether the scatter about the mean tends to remain constant with increasing age and increasing mean cholesterol. Inspection of a scatter diagram relating age and cholesterol level showed that cholesterol values are more or less normally distributed about the mean for a given age (Fig. 3). However, as age increases, there is some tailing out of the cholesterol readings in the direction of higher values. Not only is there an increase in the upper limit of the range but also an increase in the proportion of high readings (See Tables IX, X, and XI).

TABLE IX. CHOLESTEROL DATA FOR MEN AT DIFFERENT AGES BASED ON FIRST TEST

AGE	N	MEAN CHOLESTEROL	95% CONFIDENCE LIMITS FOR THE MEAN	STANDARD DEVIATION (s)	RANGE	COEFFICIENT OF VARIATION $= \frac{s}{\text{MEAN}} \times 100\%$	
19	4	212.2	199.0	34.8	122–285	16.6	
20	38	209.6	220.7				
	42	209.8					
21	90	220.5	212.4 228.6	38.8	152–320	17.6	16.7
22	131	229.3	223.0 235.6	36.4	150–350	15.9	
23	88	228.8	218.9 238.7	46.8	108–378	20.5	
24	50	236.4	224.5 248.4	42.0	163–360	17.8	18.5
25	49	220.4	209.6 231.3	37.9	135–355	17.2	
26	38	232.5	216.3 248.8	49.3	140–340	21.2	
27	10	227.8	199.1 256.6	40.2	177–308	17.7	19.6
28	13	261.2					
29	10	228.9					
30	16	237.7	236.6	50.0	163–390	20.2	
31	8	241.5	262.8				
32	6	288.7					
33	5	266.0					
	58	249.7					
19–33	556	228.5					

The problem of scatter about the mean was more thoroughly examined in terms of standard deviations for each age (Table IX). Bartlett's test of homogeneity of variances was inconclusive. However, there appears to be some increase in the size of the standard deviations as both age and mean cholesterol go up. The coefficients of variation also reflect this trend, and on the average the standard deviation is increasing faster than the mean cholesterol (Table IX).

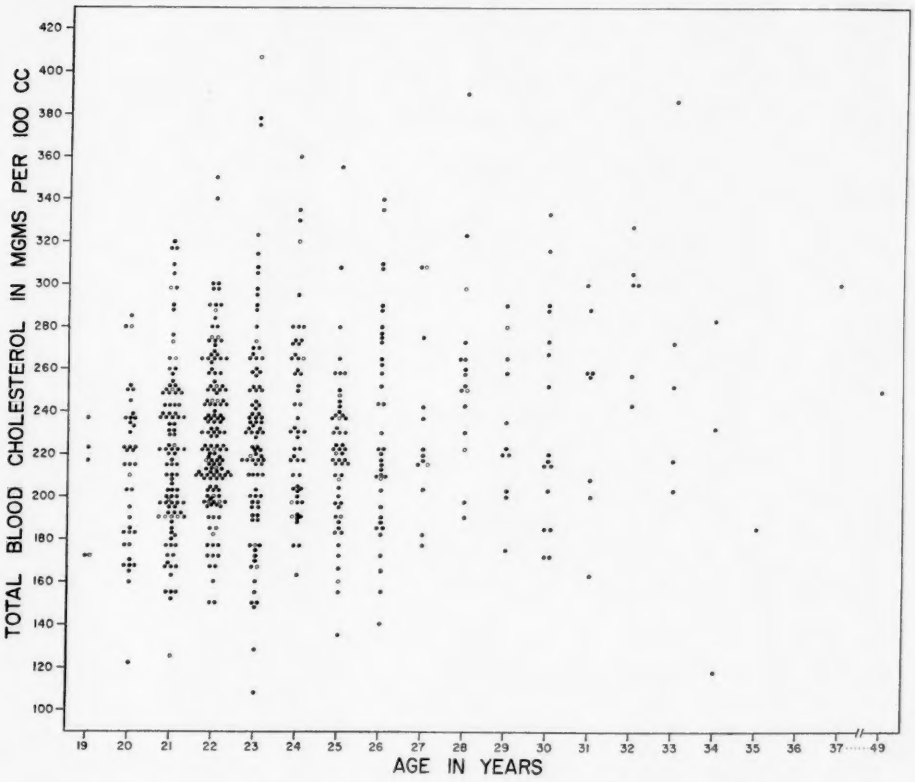

Fig. 3.—Scatter diagram of first cholesterol determinations of 612 medical students arranged according to age. ● = Men. o = Women.

The standard deviation is an important population parameter which describes the variability of the subjects about the group mean in a normally distributed population of cholesterol readings. For our 556 men 19 to 33 years of age, the standard deviation is calculated to be 42.5 mg. per 100 c.c. Our standard deviations lie between 34.8 and 50.0 mg. per 100 c.c. for this age span. Investigators using different laboratory methods, which result in slightly different mean levels, and working with different populations have obtained roughly the same kind of within-group variability estimates for cholesterol. Table XII shows that our data at various ages are in keeping with the findings of others at somewhat similar ages. Only Keys has an equally large series, and while his figures tend to be lower than ours, they show a similar tendency to go up with increasing age.[18]

Thus far we have considered the relationship of age to cholesterol level as shown by different subjects at varying ages at the time of the first cholesterol determination. We also have data based on two tests on the same individual at different ages. Only the first cholesterol reading appeared in the analysis of the relationship of age of 556 male subjects to cholesterol level; the second cholesterol reading is new information for 201 of these same individuals. Additional data on 109 subjects from the classes of 1958 and 1959 were introduced, providing new material on both the first and second cholesterol values. The total number of different individuals with two tests studied here is 310.

If the significant age groups in Table X, i. e., 19-20, 21, 22-27, and 28-33, have validity, then groups of individuals moving from one age group to another should show predictable changes in their mean cholesterol level (according to the results of Table X). This would provide an independent check on Table X

TABLE X. MEAN CHOLESTEROL LEVELS FOR SIGNIFICANT AGE GROUPS IN JOHNS HOPKINS MEN

AGE	N	MEAN CHOLESTEROL	95% CONFIDENCE LIMITS FOR THE MEAN	STANDARD DEVIATION (s)	RANGE
19-20	42	209.8	199.0 220.7	34.8	122–285
21	90	220.5	212.4 228.6	38.8	152–320
22-27	366	229.3	225.0 233.5	41.6	108–378
28-33	58	249.7	236.6 262.8	50.0	163–390

Result of "t" Tests

AGE	21	22–27	28–33
19 and 20	NS	$.001 < P < .01$	$P < .001$
21		NS	$P < .001$
22-27			$.001 < P < .01$

$$t = \frac{|\text{Mean}_1 - \text{Mean}_2|}{\sqrt{\text{S.E.}^2_{M_1} + \text{S.E.}^2_{M_2}}}$$

where $\text{S.E.}_{\text{Mean}_1} = \frac{s_1}{\sqrt{N_1}}$

NS = Mean cholesterols for the two age groups are not significantly different using P = .05 as the level of significance.

P = Probability that a difference between the means for the two age groups as large as that observed or larger will arise by chance when the null hypothesis is that there is no difference between the means.

TABLE XI. RELATIONSHIP OF AGE TO CHOLESTEROL LEVEL: PER CENT OF MEN AT GIVEN AGE AT FIRST TEST FOR THREE CLASSES OF FIRST CHOLESTEROL LEVELS

AGE OF MEN AT FIRST TEST	19 AND 20	21	22	23	24 AND 25	26 AND 27	28 TO 33	TOTAL
Number of men at given age	42	90	131	88	99	48	58	556
Per cent of men at given age with first cholesterol level in mg. %								
<200	38.1	33.3	17.6	22.7	24.2	25.0	13.8	23.9
200–249	50.0	42.2	55.0	48.9	48.5	41.7	31.0	46.8
≧ 250	11.9	24.4	27.5	28.4	27.3	33.3	55.2	29.3
	100.0	99.9	100.0	100.0	100.0	100.0	100.0	100.0

TABLE XII. ESTIMATES OF STANDARD DEVIATIONS FOR NORMAL MALE POPULATIONS OF DIFFERENT AGES BY OTHER INVESTIGATORS COMPARED WITH THE JOHNS HOPKINS DATA

AUTHORS	LABORATORY METHOD	N	AGE	MEAN CHOLESTEROL LEVEL	STANDARD DEVIATION
				mg. %	
Collen[32] as computed by Keys[18]	Bloor	36	30–39	242.0	37.0*
Keys[18]	Schoenheimer-Sperry and Bloor	168	18†	168.2‡	30.7
		145	20†	173.7‡	32.0
		163	25†	184.4‡	34.0
		142	30†	195.1‡	40.3
		56	35†	200.4‡	43.1
Katz, Rhodes, George, and Moses[6]	Schoenheimer-Sperry	17	33†	202	48.0
Gertler and White[7]	Bloor	7	20–29	230.0	31.8*
		53	30–39	227.0	36.4*
Adlersberg[22]	Schoenheimer-Sperry	22	18–22	185.2	55.2*
		16	23–27	194.5	39.0*
		38	28–32	243.1	49.4*
Johns Hopkins data (from Table X)	Bloor	42	19–20	209.8	34.8
		90	21	220.5	38.8
		366	22–27	229.3	41.6
		58	28–33	249.7	50.0

*The standard deviation was estimeated by us from the sample size N and S_{Mean} as given.
†Mean age.
‡The mean cholesterol level was based on larger numbers than are given in column N.

from a different point of view. Despite the problems of small numbers and/or short time intervals between tests for certain groups, we have analyzed 12 independent samples of information ranging in size from N = 17 to N = 39. Table XIII summarizes the results. We found that two different groups of 21 year olds at first test had a significant rise in mean cholesterol level after an interval

TABLE XIII. AGING EFFECT: ACTUAL OCCURRENCE OF RISE IN CHOLESTEROL LEVEL AT SECOND TEST

	CLASS	1959*	1958	1948–1957		
	TIME ELAPSED	<7 MONTHS	<8 MONTHS	<12 MONTHS	12-18 MONTHS	36-47 MONTHS
Aged 21 at first test	$\bar{C}_1$	210.4	225.8	222.7	220.2	216.4
	$\bar{C}_2$	222.6	217.5	219.4	240.0	241.9
	$\bar{D}$	+12.2	−8.2	−3.3	+19.8	+25.6
	N	25	26	17	23	18
	Range	−50 to +100	−110 to +43	−40 to +73	−30 to +107	−32 to +128
	P	NS	NS	NS	.01 < P < .02	.01 < P < .02
	% of subjects with:					
	rise	76%	38%	18%	65%	72%
	no change	0%	12%	29%	0%	11%
	fall	24%	50%	53%	35%	17%
Aged 22 at first test	$\bar{C}_1$	211.0	234.6	235.9	236.2	237.8
	$\bar{C}_2$	218.5	219.1	227.2	251.1	229.2
	$\bar{D}$	+7.5	−15.5	−8.7	+14.8	−8.6
	N	30	28	20	30	17
	Range	−103 to +86	−102 to +44	−63 to +70	−76 to +103	−66 to +52
	P	NS	NS	NS	NS	NS
	% of subjects with:					
	rise	50%	39%	30%	73%	41%
	no change	10%	4%	0%	0%	6%
	fall	40%	57%	70%	27%	53%
Aged 23-26 at first test	$\bar{C}_1$			242.4	238.0	
	$\bar{C}_2$			235.8	230.5	
	$\bar{D}$			−6.6	−7.5	
	N			37	39	
	Range			−83 to +122	−125 to +88	
	P			NS	NS	
	% of subjects with:					
	rise			41%	51%	
	no change			0%	5%	
	fall			59%	44%	

*Including one woman.

$\bar{C}_1$ = Mean of first cholesterol levels

$\bar{C}_2$ = Mean of second cholesterol levels

$\bar{D}$ = Average difference (Chol. 2-Chol. 1) for the group obtained as an average of all the individuals' differences.

N = Number of male subjects

Range = Range of (Chol. 2-Chol. 1) differences for the group

P = Probability that an average difference for the group as large as that observed or larger could arise by chance when sampling from a universe whose mean is o.

P is associated with $t = \frac{|\bar{D} - O|}{S.E._{\bar{D}}}$ and the degrees of freedom (N-1). P > .05 is not considered statistically significant (NS).

of 12 to 18 months and 36 to 47 months, which made them 22 to 22½ and 24 to 25 years old, respectively. However, not all the individuals in each of these two groups responded in the same way. Some showed a rise, some had no change, and some showed a decrease in cholesterol level. To be noted are the variability in the average differences, the large range of differences, the magnitude of both the positive and negative extreme values, and the variable per cent of individuals with rise in cholesterol in all the groups where no change in the mean cholesterol

level would be expected. Considerably larger groups with two tests on each individual would have to be studied for much longer periods of time to check the "aging effect" with some degree of sureness. This emphasizes the fact again that the effect of aging on cholesterol level is best recognized as a large group phenomenon and there is no predicting what an individual's pattern will be.

Limited studies were conducted on the effect of age on cholesterol level in women. Because of the small number of observations at each age, comparison with the men could be made only at ages 21, 22, and 22-27 inclusive (Table XIV). It is apparent that at these ages the data on the mean cholesterol levels of the men and women are in statistical agreement. This is in keeping with Adlersberg's findings that there is no significant difference between the sexes at these ages.[44]

TABLE XIV. COMPARISON OF CHOLESTEROL LEVELS OF MEN AND WOMEN AT DIFFERENT AGES

AGE	SEX	N	MEAN CHOLESTEROL	95 % CONFIDENCE LIMITS FOR THE MEAN	s
21	Men	90	220.5	212.4–228.6	38.8
	Women	12	217.7	187.4–247.9	47.6
22	Men	131	229.3	223.0–235.6	36.4
	Women	14	227.6	207.6–247.7	34.7
22–27	Men	366	229.3	225.0–233.5	41.6
	Women	31	232.4	213.4–251.3	51.8

In order to study further the effect of age on the behavior of cholesterol in a given individual, we have redetermined the cholesterol level of 30 of our subjects, both men and women, 4 to 8 years after the initial measurements.* The data are presented in Table XV. After a lapse of years, 11 subjects showed higher levels, 17 subjects showed lower levels, and 2 subjects showed no change. These results are similar to the findings of Sperry and Webb, who re-examined 14 men and 8 women 14 years after their first observation.[48] The fact that their cholesterol method had been changed somewhat during the interval made precise comparison difficult or impossible, but it appeared that, as in our series, some cholesterol levels went up, some stayed the same, and some decreased a little. They concluded that "serum cholesterol increases with age in some persons, but the increase is not an obligatory circumstance of aging."

Man and Peters came to essentially the same conclusion upon remeasuring cholesterol levels on 16 subjects after intervals of 10 to 20 years.[49] Their subjects, of both sexes and 20 to 48 years of age at first test, showed no consistency in the direction of change of any of the lipid components. "Although they rose significantly more frequently than they fell, this tendency was not sufficiently preponderant to warrant the deduction that it is characteristic of the aging process."

*Blood samples were obtained from members of the Johns Hopkins Hospital house staff on a voluntary basis. There was definite selection in regard to subjects previously found to be hypercholesteremic, so that this group does not represent a random sample.

TABLE XV. REDETERMINATION OF THE CHOLESTEROL LEVEL IN THIRTY SUBJECTS AFTER AN INTERVAL OF FOUR TO EIGHT YEARS

SUBJECT NO.	AGE		TIME LAPSE IN YEARS	CHOLESTEROL IN MG. %		
	FIRST TEST	LAST TEST		FIRST TEST	LAST TEST	DIFFERENCE
52168	20	28	8	223	200	− 23
54170*	21	26	5	317	233	− 84
55235*	21	26	5	298	176	−122
55153	21	26	5	203	207	+ 4
52206	21	29	8	190	194	+ 4
52230	21	29	8	190	172	− 18
55126*	22	26	4	237	204	− 33
55134	22	27	5	258	254	− 4
51167	22	28	6	220	220	0
52173	22	28	6	252	250	− 2
54130*	22	28	6	280	269	− 11
49155	22	29	7	213	214	+ 1
51151	22	29	7	215	248	+ 33
51284	22	29	7	200	217	+ 17
52176*	22	29	7	290	290	0
53150*	22	29	7	340	303	− 37
52165*	22	30	8	190	224	+ 34
55159*	23	28	5	265	277	+ 12
50165	23	29	6	270	166	−104
53176*	23	30	7	288	460	+172
53129	24	28	4	203	247	+ 44
55130	24	28	4	243	230	− 13
50251*	24	29	5	320	273	− 47
54121*	24	30	6	355	269	− 86
52145	26	33	7	165	230	+ 65
49228	27	31	4	308	250	− 58
50163	27	32	5	275	210	− 65
53153	28	33	5	243	188	− 55
51129	29	33	4	203	177	− 26
52155*	31	39	8	300	365	+ 65

*Also see Table XVI.

We have demonstrated that as age advances, there is an increasing proportion of hypercholesteremia in the total population (Fig. 4).[45] However, just how and when such a marked elevation of cholesterol level comes about in a given individual is not yet clear. Only one (Subject 53176) of the 30 subjects re-examined after 4 to 8 years showed an increase in cholesterol level from below to above 300 mg. per 100 c.c., while 4 of the 6 subjects whose cholesterol levels were initially 300 mg. per 100 c.c. or more showed values below 300 mg. per 100 c.c. at the final test (Table XV). It is to be noted particularly that, after such a time lapse, 13 of 30 (43 per cent) had differences smaller than ±25 mg. per 100 c.c., which is in the realm of laboratory error.

It is of interest to examine the degree of change observed among the subjects with high and low levels at the initial determination. There were 18 subjects whose cholesterols at first test were under 270 mg. per 100 c.c. Four to 8 years later, only 2, or 11.1 per cent, showed changes greater than ±45 mg. per 100 c.c., and none had changes greater than ±65 mg. per 100 c.c. In contrast, of the 12 subjects whose initial cholesterols were 270 mg. per 100 c.c. or above, all

but 3, or 75.0 per cent, showed changes in one direction or the other greater than ±45 mg. per 100 c.c. at the end of 4 to 8 years. Accordingly, the great majority of those with initially low cholesterol levels showed relatively little variation, while those with higher cholesterol levels showed much greater variability. That this observation may be important from the point of view of the individual is apparent when it is recalled that, on the average, higher cholesterol levels and greater cholesterol variability distinguish patients with coronary artery disease from control subjects.[25,26,28-35] If "precoronary" individuals are to be identified, metabolic patterns reflected by differences in level and stability of total serum cholesterol in the third and fourth decade may prove of value as an aid in the selection of subjects who have increased susceptibility to future coronary attacks.

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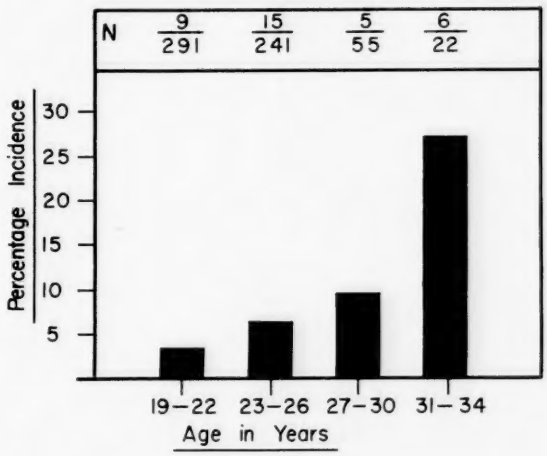

Fig. 4.—Incidence of hypercholesteremia at first test among 609 subjects grouped according to age. (From Thomas, C. B.: Am. J. M. Sc. **232**:389, 1956. By permission of Lea & Febiger.)

Little more is added to our understanding of these problems by a review of all the data on the 49 subjects in the classes of 1948-1957 who had three or more cholesterol determinations, whether over longer or shorter periods of time (Table XVI). Some individuals (e.g., Subjects 55134, 55159, 54130, and 52176) had remarkably little change in cholesterol level on repeated tests while others presented a picture of wide variability over a period of 5 to 7 years (e. g., Subjects 53176 and 54170). These subjects can be matched by individuals with similarly stable or variable cholesterol levels over a time period of a year or less (e. g., Subjects 52175, 53136, 50152, and 53128 [stable] compared with 49105 and 50242 [labile]). A small group appeared to show a consistent trend toward higher levels with increasing age (e. g., Subjects 50138, 52110, 57109, 57103, 57133, 57134, 51170, and 51134). However, in most of these subjects, the time lapse was relatively short. In contrast to a consistent trend toward higher levels, some individuals showed a well-marked decrease in cholesterol level over a period of 5 or 6 years (e. g., Subjects 55235 and 54121). It is clear that considerably more data on each individual would be necessary before we could

TABLE XVI. MULTIPLE CHOLESTEROL DETERMINATIONS ON THE SAME INDIVIDUALS (ALL WHO HAD THREE OR MORE TESTS, CLASSES OF 1948-1957)

INITIAL CHOLESTEROL LEVEL	SUBJECT NO.	CHOLESTEROL IN MG. PER 100 C.C.					AGE					TOTAL TIME IN YEARS
		1	2	3	4	5	1	2	3	4	5	
A. Under 200 mg. per 100 c.c.	52175	160	172	182	—	—	20	20	20	—	—	<1
	54152	190	190	177	—	—	21	22	22	—	—	1
	51103	108	170	132	—	—	23	24	24	—	—	1
	50138	118	148	208	—	—	34	34	35	—	—	1
	52110	183	194	288	280	—	20	21	22	22	—	2
	52149	190	182	215	—	—	20	21	22	—	—	2
	57132	177	217	200	—	—	19	21	22	—	—	3
	52135	170	123	128	203	—	20	22	22	24	—	4
	49131	122	158	163	144	175	20	21	21	21	24	4
	52165	190	194	250	224	—	22	23	24	30	—	8
B. 200-249 mg. per 100 c.c.	53136	200	182	200	—	—	21	21	21	—	—	<1
	53168	200	265	222	—	—	21	22	22	—	—	1
	57101	217	197	210	—	—	21	22	22	—	—	1
	53175	208	158	215	—	—	22	22	23	—	—	1
	57109	217	230	273	—	—	22	22	23	—	—	1
	57144	244	258	258	—	—	22	23	23	—	—	1
	57153	217	200	237	—	—	22	23	23	—	—	1
	57103	210	210	308	—	—	21	22	23	—	—	2
	49222*	214	175	204	173	208	22	22	23	23	24	2
	57122	217	222	230	—	—	22	23	24	—	—	2
	57133	203	266	277	—	—	20	22	23	—	—	3
	57102	237	222	217	230	—	20	22	22	23	—	3
	57154	210	222	207	—	—	22	23	25	—	—	3
	55126	237	203	204	—	—	22	25	26	—	—	4
	55153	203	250	207	—	—	21	25	26	—	—	5
C. 250-299 mg. per 100 c.c.	49105	272	170	235	—	—	24	24	24	—	—	<1
	50122	252	295	330	275	274	30	30	30	31	31	1
	57134	250	265	298	—	—	22	23	24	—	—	2
	55235*	298	234	176	—	—	21	25	26	—	—	5
	55134	258	263	254	—	—	22	26	27	—	—	5
	55159	265	289	277	—	—	23	27	28	—	—	5
	54130	280	265	269	—	—	22	23	28	—	—	6
	52176	290	297	290	—	—	22	23	29	—	—	7
	53176	288	172	344	460	—	23	24	26	30	—	7
D. 300 mg. per 100 c.c. or over	50152	305	304	283	—	—	23	23	23	—	—	<1
	53128	360	350	350	—	—	24	24	24	—	—	<1
	50242*	407	228	408	—	—	23	24	24	—	—	1
	53137	330	280	272	—	—	24	25	25	—	—	1
	50155	390	416	327	—	—	28	29	29	—	—	1
	50170	323	297	380	—	—	28	28	29	—	—	1
	51170	333	400	410	—	—	30	31	31	—	—	1
	50172	300	314	245	—	—	31	32	32	—	—	1
	51134	309	330	340	—	—	21	23	23	—	—	2
	56125	335	273	325	—	—	24	25	27	—	—	3
	54170	317	172	335	233	—	21	21	24	26	—	5
	50251*	320	280	273	—	—	24	24	29	—	—	5
	54121	355	308	269	—	—	24	25	30	—	—	6
	53150	340	434	303	—	—	22	24	29	—	—	7
	52155	300	383	365	—	—	31	32	39	—	—	8

*Female subject.

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distinguish between changes related to the "aging effect," whatever that may be, in certain individuals and those referable to technical and biologic variability.

C. *Total Variability of Cholesterol Level.*—Finally, we have looked at the Johns Hopkins cholesterol data from the point of view of total variability. The total variability of cholesterol level found in successive determinations in a given individual represents the algebraic sum of all forms of technical and biologic variability.[20] Thus far, we have demonstrated that the components contributed by technical error and by the "aging effect" among our group of subjects are relatively small. On the average, the technical error of measurement of cholesterol determinations carried out in the Johns Hopkins Hospital Chemistry Laboratory amounts to approximately 11 mg. per 100 c.c. (Table II). In studying the effect of age, we have shown that while there is a *mean* increase in cholesterol level of nearly 3 mg. per 100 c.c. per year of age between the ages of 19 and 33 years in men, the "aging effect" is not equally distributed at all ages or among all individuals. Between the ages of 22 and 27, there is no significant increase of mean cholesterol with age. Also, over a time lapse of 4 to 8 years, only 6 of 30 subjects (20 per cent) showed appreciable rises in cholesterol level.

TABLE XVII. CORRELATION COEFFICIENTS AS AN EXPRESSION OF THE AMOUNT OF AGREEMENT BETWEEN TWO CHOLESTEROL DETERMINATIONS PER INDIVIDUAL, WITH VARYING TIME LAPSES, FOR GROUPS OF JOHNS HOPKINS MEDICAL STUDENTS

DERIVATION OF PAIRS OF CHOLESTEROL DETERMINATIONS	TIME LAPSE BETWEEN TWO DETERMINATIONS	$r^* \pm s_r$	N	CONTRIBUTING CLASSES	AVERAGE AGE AT FIRST TEST	AGE RANGE AT FIRST TEST
A. Two tests on the same individual† (men only)	< 7 months	0.66 ± .07	71	1959	21.9	19 to 28
	< 12 months	0.64 ± .05	157	1949-1958‡	22.9	19 to 34
	12-18 months	0.61 ± .06	111	1949-1955, 1957	22.8	19 to 34
	36-47 months	0.56 ± .10	51	1949, 1951-1955	21.9	19 to 29
B. Three tests on the same individual (men and women)	I vs. II 2- 7 months II vs. III 5-10 months I vs. III 12-13 months	0.65 ± .07 0.76 ± .05 0.64 ± .07	48	1958§	22.4	20 to 34

*All of these r's are significantly different from 0 at the 1 per cent level of significance in terms of the sample size N, when testing the null hypothesis that $r = 0$.[50]

When	then r at 1% level of significance is:
$N - 2 = 45$	0.37
$N - 2 = 90$	0.27
$N - 2 = 150$	0.21

†The groups of individuals are different for the four time periods; therefore, these are all independent estimates of correlations between two cholesterol determinations.

‡93 paired observations were from individuals in the classes of 1949-1957; 64 were from 1958.

§43 of the paired observations I versus II appear in the 64 pairs from the class of 1958 cited above.

Fig. 5 *A*, *B*, and *C* presents visually the relationship of two cholesterol determinations on the same subject, with time lapses between determinations of less than 12 months, 12 to 18 months, and 36 to 47 months inclusive. These three graphs show that there is a linear relationship between the first and second cholesterol determinations but that there is considerable scatter at all levels about a line of exact agreement. Pearson product-moment coefficients of correlation and their standard errors ($r \pm s_r$) were derived for these groups of data and for others with varying time lapses, all of which are summarized in Table XVII.

Using the correlation coefficient for duplicate determinations on the same serum sample, r = 0.92 ± 0.01, as a frame of reference, we found that our correlation coefficients, with time lapse adding the effects of biologic variation to that of technical error, have reached a much lower level. In the first series of correlations, the most prominent observation is the amount of general agreement between the r's, whether less than 7 months has passed or 3 to 4 years (Table XVII). It is true that r becomes a little smaller with larger lapses of time, but the four r's are in statistical agreement in terms of their standard errors for groups of this size. The Gofman group, using the Schoenheimer-Sperry method and working with a middle-aged male population, obtained r = 0.75 ± 0.07 (N = 45) for the coefficient of reliability for one determination correlated with a second over one year's time, a figure in statistical agreement with ours.[47,51]

TABLE XVIII. PER CENT DISTRIBUTION OF DIFFERENCES FOR FIRST CHOLESTEROL VALUES 150-299 MG. PER 100 C.C. FOR DUPLICATE CHOLESTEROL DETERMINATIONS FROM SAME SERUM SAMPLE AND FOR TWO CHOLESTEROL DETERMINATIONS WITH TIME LAPSE BETWEEN THEM

	DUPLICATE CHOLESTEROL DETERMINATIONS FROM SAME SERUM SAMPLE*		TWO CHOLESTEROL DETERMINATIONS WITH TIME LAPSE OF	
CHOLESTEROL 2—CHOLESTEROL 1 (MG. %)	SERIES 1 1955	SERIES 2 1956	<12 MONTHS	12-47 MONTHS
Difference of 0	36.8	26.4	7.4	3.2
Differences between and including: ±1 and ±25	94.7† 57.9	94.5 68.1	63.1 55.7	52.6 49.4
±26 and ±50	1.3	2.8	25.1	22.1
±51 and ±75	2.6	2.8	7.4	14.3
±76 and ±100	1.3	—	3.0	8.4
Differences over ±100	—	—	1.5	2.5
Total Per cent	99.9	100.1	100.1	99.9
Number of Subjects	76*	72	203	154

*See Tables I-III.

†For series 1, if the two pairs of dubious observations are included making N = 78 the per cent of differences ± 25 mg. per cent or less is then 92.3.

It is to be noted that the independent estimate of r = 0.66 for the class of 1959 with a time lapse of less than 7 months agrees with r = 0.64 for the classes 1949-1958 with a time lapse of less than 12 months. Our data are notably consistent. In the special instance where we have three cholesterol determinations on the same individual for the class of 1958, the correlation coefficients are of the right order of magnitude (Table XVII *B*). The value r = 0.65 for Tests I versus II (time lapse 2 to 7 months) is in good agreement with r = 0.66 for the class of 1959 (time lapse <7 months, Table XVII *B* versus *A*). Second and third determinations gave a slightly higher r, but r = 0.76 is in statistical agreement with r = 0.65 and r = 0.64.

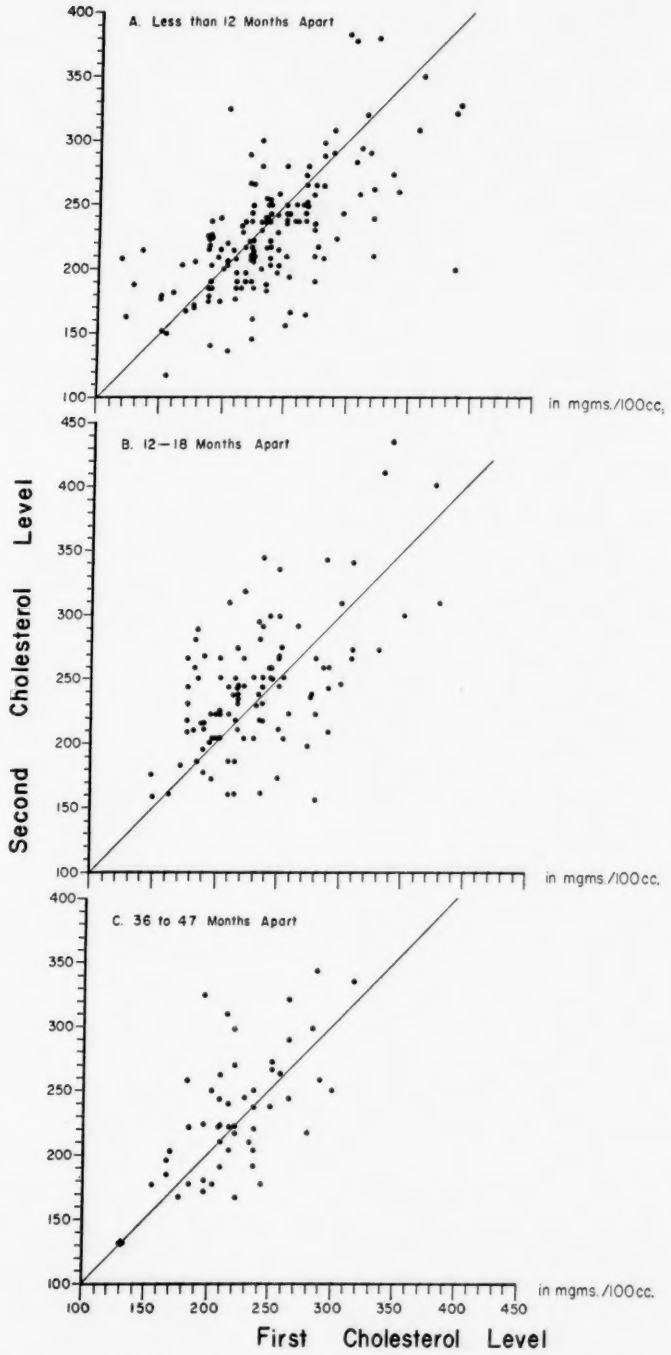

Fig. 5.—Relationship between two cholesterol determinations in the same individual after different intervals of time. Correlation coefficients for graphs *A*, *B*, and *C* are r = 0.64 ± 0.05, r = 0.61 ± 0.06, and r = 0.56 ± 0.10, respectively. (See Table XVII.)

Correlation coefficients, divorced from the graphs which indicate the kind of linear relationship, the degree of scatter of the observations about the line, and the numerical values of the cholesterol data, do not tell the whole story. It was thought that it might make the same data more meaningful to present in summary fashion the kind of numerical differences that appeared between two cholesterol determinations (Cholesterol 2 — Cholesterol 1) and what proportion of the time they did appear (Table XVIII). In the main, the differences were distributed about zero, with about equal likelihood of being either positive or negative. There was a small shift toward the positive differences for the 36-47 months group.

TABLE XIX. PER CENT DISTRIBUTION OF DIFFERENCES, FOR LOW AND HIGH FIRST CHOLESTEROL VALUES, FOR TWO CHOLESTEROL DETERMINATIONS WITH A TIME LAPSE BETWEEN THEM UP TO 47 MONTHS

CHOLESTEROL 2—CHOLESTEROL 1 (MG. %)		FIRST CHOLESTEROL LEVEL		
		100–149 MG. %	300–349 MG. %	350–399 MG. %
Difference of O		—	—	—
Differences between and including:	± 1 and ±25	25.0	25.0	25.0
	±26 and ±50	25.0	25.0	12.5
	±51 and ±75	25.0	25.0	50.0
	±76 and ±100	25.0	20.8	—
Differences over ±100		—	4.1	12.5
Total per cent		100.0	99.9	100.0
Number of subjects		8	24	8

Table XVIII shows the per cent distribution of (Cholesterol 2—Cholesterol 1) differences, for subjects with initial cholesterol values of 150 to 299 mg. per 100 c.c. first for the two series of duplicate determinations from the same serum sample (described under Reliability of Method) and then for two cholesterol determinations with time lapses of less than 12 months and 12 to 47 months. The following relationships were noted:

1. Whereas 26 to 37 per cent of the paired cholesterol determinations from the same serum sample are in exact agreement in the two series, there is a diminished incidence of zero differences (7 per cent and 3 per cent) when the second determination is separated from the first by an interval of time.

2. In the two series of duplicate determinations, only 5 per cent of the differences are larger than ±25 mg. per 100 c.c. However, when up to 12 months have passed, 37 per cent of the differences are larger than ±25 mg. per 100 c.c., and when 12 to 47 months have passed, 47 per cent of the differences are outside that range.

3. About one quarter of the differences between two independent cholesterol determinations, whether separated by a period of months or one to four years lie between ±26 and ±50 mg. per 100 c.c., as compared with 1 to 3 per cent in the two series of duplicate determinations.

4. Differences larger than ±75 mg. per 100 c.c. are much more prominent in the time lapse studies.

5. The proportion of large differences beyond ±50 mg. per 100 c.c. increases when 12 to 47 months have passed as compared with less than 12 months.

Differences larger than ±25 mg. per 100 c.c. between two cholesterol determinations separated by a period of months therefore usually appear to be due to biologic variability. This table shows the kind of normal variation that exists between two cholesterol determinations with the passage of time.

We have very little data for (Cholesterol 2 − Cholesterol 1) differences for first cholesterol levels of 100-149 mg. per 100 c.c. and over 300 mg. per 100 c.c.; accordingly, the data for all time intervals up to 47 months have been pooled (Table XIX). While the numbers are small, it appears that there may be increased variability where subjects have very high or very low initial levels. (Compare Table XIX with Table XVIII.)

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TABLE XX. ESTIMATES OF THE STANDARD ERROR FROM PAIRED DETERMINATIONS AS A MEASURE OF TOTAL VARIABILITY (s_T)*: TIME LAPSES UP TO 12 MONTHS BETWEEN TWO TESTS

FIRST CHOLESTEROL LEVEL (MG. %)	CUMULATIVE NUMBER OF INDIVIDUALS CONTRIBUTING PAIRS OF TESTS AT EACH LEVEL				s_T* FOR			
	<5 MONTHS	<6 MONTHS	<7 MONTHS	<12 MONTHS	<5 MONTHS	<6 MONTHS	<7 MONTHS	<12 MONTHS
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) 150–199	26	37	47	51	21.0	21.7	21.7	21.9
(2) 200–249	32	68	87	105	15.0	20.9	20.0	21.3
(3) 250–299	23	31	40	47	30.4	32.6	30.0	29.7
(1)-(3) 150–299	81	136	174	203	22.2	24.2	23.1	23.6
All data 100 to 399	93	153	194	228	27.7	28.5	27.1	27.6

*s_T was computed in the same way as s_e in the footnote of Table II.

For the final discussion of the paired data, already analyzed by correlation coefficients and differences, first cholesterol levels of 150-199, 200-249, and 250-299 mg. per 100 c.c. will be designated levels (1), (2), and (3), respectively. As was seen in the section on Reliability of Method, the technical error of measurement (s_e) for duplicate determinations for levels (1), (2), and (3) were 6.4, 10.1, and 14.0 mg. per 100 c.c., respectively (Table III). There seemed to be a rise of technical error with cholesterol level. When there has been a lapse of time between two tests on the same individual, the standard errors as a measure of total variability (s_T) go up at each level when compared with the corresponding s_e estimates. After a lapse of time of less than 12 months, s_T is 21.9, 21.3, and 29.7 for levels (1), (2), and (3) (Table XX, columns 4 and 8). Consideration of smaller periods of time does not make any sizable difference in the s_T estimates. The s_T for level (3) tends to be higher than those for the other two levels. Two cholesterol determinations less than 12 months apart seem to be in as good agreement as two determinations less than 6 months apart. The Watkin group

found that total variability of cholesterol did not increase with level for their group of subjects, most of whom were in much older age brackets than ours.[20] Moreover, their longest period of observation of cholesterol variation was 6 months.

The data in Table XXI are based on entirely independent information, and the individuals who contribute to it do not appear in Table XX. Table XXI indicates that a lapse of time of 12 to 18 months increases the size of s_T for levels (1), (2), and (3) over those values for shorter periods of time. The data for 12 to 47 months are not different from those for 12 to 18 months alone. The s_T for level (1) is now as large as that for level (3) for the data with time lapse of one year or longer.

TABLE XXI. ESTIMATES OF THE STANDARD ERROR FROM PAIRED DETERMINATIONS AS A MEASURE OF TOTAL VARIABILITY (s_T)*: TIME LAPSES 12 TO 18 MONTHS AND 12 TO 47 MONTHS BETWEEN TWO TESTS

FIRST CHOLESTEROL LEVEL (MG. %)	CUMULATIVE NUMBER OF INDIVIDUALS CONTRIBUTING PAIRS OF TESTS AT EACH LEVEL		s_T* FOR	
	TIME: 12 to 18 MONTHS	12 to 47 MONTHS	12 to 18 months	12 to 47 MONTHS
(1) 150 to 199	24	37	34.7	34.7
(2) 200 to 249	51	80	27.3	27.0
(3) 250 to 299	23	37	37.4	33.6
(1)-(3) 150 to 299	98	154	31.8	30.7
All data 100 to 399	111	170	32.4	31.2

*s_T was computed in the same way as s_e in the footnote of Table II.

Speaking in regard to a one-year period, the Gofman group has said for their middle-aged male population (with mean cholesterol of 243.0 mg. per cent) that "a single measurement places an individual (including both biologic variation and technical error) within . . . ±26 mg. per cent cholesterol of the 'true' value(s) two-thirds of the time."[47] From our studies on the same point, for a period of less than 12 months, we can say in regard to total variability, including both biologic variation and technical error, that a single cholesterol determination places an individual with an initial level of 200 to 249 mg. per 100 c.c. within ±21.3 mg. per 100 c.c. of the true value two-thirds of the time. For a period of 1 to 4 years, we have found that a single cholesterol determination places such an individual within ±27.0 mg. per 100 c.c. of the true value two-thirds of the time. These findings agree extremely well with those of the Gofman group.

For cholesterol levels between and including 150 to 299 mg. per 100 c.c., the average s_e is equal to 10.2 mg. per 100 c.c. (Table III). On the average, biologic variability, added to the effects of technical error, raises the estimate of total variability (s_T) to 23.6 mg. per 100 c.c. over periods of less than 12 months and to 30.7 mg. per 100 c.c. over lapses of 12 to 47 months. Thus s_T is now two to

TABLE XXII. THREE CHOLESTEROL DETERMINATIONS ON 49 SUBJECTS IN THE CLASS OF 1958

INITIAL CHOLESTEROL LEVEL	SUBJECT NO.	CHOLESTEROL IN MG. PER 100 C.C.			
		1	2	3	MEAN
A. Under 200 mg. per 100 c.c.	58116	188	226	197	203.7
	58121	188	174	172	178.0
	58122	150	179	160	163.0
	58128	197	240	265	234.0
	58132	177	206	210	197.7
	58133	190	185	203	192.7
	58147	188	177	172	179.0
	58155	170	167	138	158.3
	58157	190	190	172	184.0
	58166	167	203	197	189.0
	58173	190	226	167	194.3
B. 200–249 mg. per 100 c.c.	58102	224	266	230	240.0
	58104	224	214	167	201.7
	58215*	204	196	197	199.0
	58117	234	237	210	227.0
	58119	244	243	265	250.7
	58124	234	254	258	248.7
	58126	214	234	230	226.0
	58127	243	197	210	216.7
	58131	234	240	273	249.0
	58136	203	206	222	210.3
	58137	224	161	133	172.7
	58238*	222	197	243	220.7
	58141	204	136	160	166.7
	58145	224	210	210	214.7
	58149	244	203	203	216.7
	58151	222	266	217	235.0
	58152	224	206	160	196.7
	58163	222	237	185	214.7
	58165	234	239	190	221.0
	58168	217	237	203	219.0
	58175	222	206	167	198.3
	58177	234	244	237	238.3
	58178	222	222	237	227.0
	58180	210	190	172	190.7
	58169	203	220	210	211.0
C. 250-299 mg. per 100 c.c.	58201*	254	243	256	251.0
	58123	290	224	177	230.3
	58125	280	298	243	273.7
	58129	266	250	317	277.7
	58140	266	164	210	213.3
	58156	275	217	222	238.0
	58167	265	272	243	260.0
	58174	265	237	273	258.3
D. 300 mg. per 100 c.c., or over	58130	320	210	210	246.7
	58134	386	321	317	341.3
	58139	320	310	280	303.3
	58148	310	294	290	298.0
	58164	320	262	273	285.0
Mean		232.6	223.2	215.4	223.7
Range		150 to 386	136 to 321	133 to 317	133 to 386

*Female subject.

three times as large as the s_e. In addition to studies of individual total cholesterol variability based on two determinations separated by a time interval, we have analyzed data from the class of 1958 where three determinations per person were systematically obtained* (Table XXII).† In these 49 men and women aged 20 through 34 years, the three tests were performed within a span of 12 or 13 months in all but one.‡ The information embodied in Table XXII has been compared with the works of two earlier investigators who used the maximum per cent deviation from the mean per subject as a quantitative expression of cholesterol variability over a period of time. Sperry, using the method of Schoenheimer and Sperry, reported on 2 to 10 determinations carried out in 25 healthy adults of both sexes 19 to 43 years of age.[4§] He found the largest maximum per cent deviation for any subject to be 12.3 per cent (individual's mean, 200.4 mg. per 100 c.c.; interval, 15 months). Turner and Steiner, using the method of Bloor, measured total serum cholesterol at weekly intervals up to 63 weeks in 10 chronically ill patients.[24] They reported the largest maximum per cent deviation from an individual's mean to be 15.4 per cent (individual's mean, 280 mg. per 100 c.c.). The largest maximum per cent deviation from the mean among our 49 subjects was 29.7 per cent (individual's mean, 246.7 mg. per 100 c.c.).

Table XXIII gives the frequency distribution for our data compared with that of Turner and Steiner, and Sperry. Our data show individuals with greater cholesterol variability. Fifty-six per cent of Sperry's data, as compared with

TABLE XXIII. THE MAXIMUM PER CENT DEVIATION FROM THE MEAN PER SUBJECT IN JOHNS HOPKINS DATA COMPARED WITH OTHER INVESTIGATORS

MAXIMUM PER CENT DEVIATION FROM THE MEAN PER SUBJECT*	SPERRY[4]	TURNER AND STEINER[24]	JOHNS HOPKINS DATA (CLASS OF 1958)
	SCHOENHEIMER-SPERRY METHOD	BLOOR METHOD	BLOOR METHOD
0– 4	14	1	7
5– 9	10	5	15
10–14	1	3	16
15–19		1	6
20–24			2
25–29			3
Total Number of Subjects	25	10	49

$$* \frac{|\text{Extreme Cholesterol Value} - \text{Mean}|}{\text{Mean}} \times 100\%$$

*The cholesterol data for 1958 resembles that of the preceding classes (Tables VI, XII, and XVII). An analysis of variance on the 1958 data gave these results: estimate of s_T for all data = 24.8 mg. per 100 c.c., estimates of s_T for groups of subjects with initial cholesterol level of less than 200, 200 to 249, 250 to 299, and 300 mg. per 100 c.c. or above are 18.1, 21.4, 31.9, and 22.6 mg. per 100 c.c., respectively.

†The multiple determinations shown in Table XVI were not included because of the element of selection regarding certain subjects, particularly those with hypercholesteremia and those from Table V.

‡For Subject 58132, the over-all time lapse was 22 months.

§Fifteen had 2 determinations only; six had 3, and four had 5 or more tests. In all but five, the total time span was less than 20 months.

10 per cent for Turner and Steiner and 14 per cent for Johns Hopkins, have values less than 5 per cent. The Turner and Steiner data resemble ours more closely. Sperry noted in his paper: "In a larger series, even greater deviations may be anticipated since there is no reason to suppose that the maximum was reached in this limited number of experiments." Our data support his anticipation.

DISCUSSION

Our studies show that healthy medical students not only vary widely as to the *height* of the total serum cholesterol level but that they appear to differ also as to the *degree of cholesterol stability*, some being stable and others labile on repeated determinations. The well-marked variation in height of cholesterol level in these young adults cannot be accounted for on the basis of the slight differences of age between most of the members of the group. Moreover, increase in age is not accompanied by a rising cholesterol level in many subjects during periods of time ranging from a few months to over eight years. It seems clear that biologic variability from causes other than aging is a conspicuous characteristic of the cholesterol levels of many young adults.

A number of biologic factors contribute to the exact level of serum cholesterol in a given individual.[52] Not only age, sex, and heredity, but racial origin, occupation, and body build have been shown to play their parts.[7,17,53,54] The increasing importance of the composition of the diet is reflected in current medical literature; high cholesterol levels have been found to be correlated with high fat intake and low cholesterol levels with low fat content of the diet.*[55-59] The influence of various forms of stress upon the cholesterol level of human subjects is beginning to be explored.[60-62] The way is open for intensive study of the many possible sources of biologic variability in healthy young adults.

SUMMARY AND CONCLUSIONS

1. Total serum cholesterol determinations have been obtained from 759 Johns Hopkins medical students on one or more occasions by a modification of the Bloor method.

2. That method, which is an adaptation designed by Dr. Mary V. Buell to meet the exacting requirements of the Clinical Chemistry Laboratory at the Johns Hopkins Hospital, is here published in detail for the first time.

3. Analysis of 148 pairs of duplicate tests from the same serum sample showed that the over-all reproducibility of the Bloor method thus controlled was very satisfactory and comparable in exactitude to that found in other laboratories using the Schoenheimer-Sperry and Abell methods.

4. The range of cholesterol levels encountered at first test among 612 students in the classes of 1948 through 1957 lay between 108 and 407 mg. per 100

*It is our impression that major differences in dietary fat intake, such as have been found by others to be linked with significant variation in mean cholesterol levels, do not exist among Johns Hopkins medical students. Of 370 unselected subjects who analyzed the composition of their diets, 12.4 per cent rated themselves as having a high fat intake compared with 14.9 per cent of the 47 hypercholesteremic subjects who submitted the same report. Low fat intake was reported by 20.3 per cent of the unselected subjects and 23.4 per cent of those with hypercholesteremia; 67.3 and 61.7 per cent of the respective groups had "average" fat intake, as compared with their fellows.

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c.c. inclusive; 92.3 per cent of these initial levels lay between 150-299 mg. per cent inclusive.

5. The mean cholesterol level for the 612 subjects at first test was 228.7 mg. per 100 c.c., with a standard deviation of ±43.3.

6. The range and mean for the 50 women were similar to the findings for the 562 men.

7. The rise of mean cholesterol level with increasing age described by others has been verified: in a group of 556 men 19 through 33 years of age, the average cholesterol level increased 2.88 mg. per 100 c.c. per year of age. Limited studies of women in their twenties suggest a similar rise.

8. When repeated determinations over a period of months or years in a given individual are considered, however, the cholesterol level does not always rise; increase with age is by no means the rule.

9. It appears that other sources of biologic variability, often exceeding the "aging effect" in magnitude, play a major role in determining the cholesterol levels of healthy subjects under the age of 35 years.

10. The meaning of total cholesterol variability in this group of subjects has been interpreted statistically from several points of view.

11. Wherever possible, statistical comparison of our findings with those of others has been made, thus constructing a series of bridges between the Johns Hopkins data and the results of many investigators as an aid to the over-all understanding of certain aspects of the cholesterol problem.

REFERENCES

1. Thomas, C. B.: Observations on Some Possible Precursors of Essential Hypertension and Coronary Artery Disease, Bull. Johns Hopkins Hosp. **89:**419, 1951.
2. Page, I. H., Kirk, E., Lewis, W. H., Jr., Thompson, W. R., and Van Slyke, D. D.: Plasma Lipids of Normal Men at Different Ages, J. Biol. Chem. **111:**613, 1935.
3. Sperry, W. M.: The Relationship Between Total and Free Cholesterol in Human Blood Serum, J. Biol. Chem. **114:**125, 1936.
4. Sperry, W. M.: The Concentration of Total Cholesterol in the Blood Serum. J. Biol. Chem. **117:**391, 1937.
5. Man, E. B., and Gildea, E. F.: Variations in Lipemia of Normal Subjects, J. Biol. Chem. **119:**769, 1937.
6. Katz, L. B., Rhodes, G. J., George, R. S., and Moses, C.: Total Serum Cholesterol, Cholesterol-Lipid Phosphorus Ratio, and S_f 12-20 Concentration in Hypertension, Diabetes, and Coronary Artery Disease, Am. J. M. Sc. **225:**120, 1953.
7. Gertler, M. M., and White, P. D.: Coronary Heart Disease in Young Adults. The Commonwealth Fund, Cambridge, Mass., 1954, Harvard University Press.
8. The Technical Group of the Committee on Lipoproteins and Atherosclerosis, and the Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council. Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis. Report of a Cooperative Study of Lipoproteins and Atherosclerosis, Circulation **14:**691, 1956.
9. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24:**227, 1916.
10. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106:**745, 1934.
11. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A Simplified Method for the Estimation of Total Cholesterol in Serum and Demonstration of Its Specificity, J. Biol. Chem. **195:**357, 1952.
12. Gardner, J. A., and Gainsborough, H.: CXXIX. Studies on the Cholesterol Content of Normal Human Plasma. Part III. On the So-called Alimentary Hypercholesterolaemia, Biochem. J. **22:**1048, 1928.
13. McClure, C. W., and Huntsinger, M. E.: Studies in Fat Metabolism. I. The Influence on Blood Lipids of Single Foodstuffs, J. Biol. Chem. **76:**1, 1928.

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14. Bruger, M., and Somach, I.: The Diurnal Variations of the Cholesterol Content of the Blood, J. Biol. Chem. **97**:23, 1932.
15. Boyd, E. M.: Diurnal Variations in Plasma Lipids, J. Biol. Chem. **110**:61, 1935.
16. Keys, A., Anderson, J. T., and Mickelsen, O.: Serum Cholesterol in Men in Basal and Nonbasal States, Science **123**:29, 1956.
17. Kornerup, V.: Concentrations of Cholesterol, Total Fat and Phospholipid in Serum of Normal Man. Report of a Study With Special Reference to Sex, Age, and Constitutional Type, Arch. Int. Med. **85**:398, 1950.
18. Keys, A., Mickelsen, O., Miller, E. O., Hayes, E. R., and Todd, R. L.: The Concentration of Cholesterol in the Blood Serum of Normal Man and Its Relation to Age, J. Clin. Invest. **29**:1347, 1950.
19. McMahon, A., Allen, H. N., Weber, C. J., and Missey, W. C., Jr.: Hypercholesterolemia. South. M. J. **44**:993, 1951.
20. Watkin, D. M., Lawry, E. Y., Mann, G. V., and Halperin, M.: A Study of Serum Beta Lipoprotein and Total Cholesterol Variability and Its Relation to Age and Serum Level in Adult Human Subjects, J. Clin. Invest. **33**:874, 1954.
21. Swanson, P., Leverton, R., Gram, M. R., Roberts, H., and Pesek, I.: Blood Values of Women: Cholesterol, J. Gerontol. **10**:41, 1955.
22. Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang, C-I.: Age, Sex, Serum Lipids, and Coronary Atherosclerosis, J.A.M.A. **162**:7, 619, 1956.
23. Schube, P. G.: Variations in the Blood Cholesterol of Man Over a Time Period, J. Lab. & Clin. Med. **22**:280, 1936-1937.
24. Turner, K. B., and Steiner, A.: A Long-Term Study of the Variation of Serum Cholesterol in Man, J. Clin. Invest. **18**:45, 1939.
25. Steiner, A., and Domanski, B.: Serum Cholesterol Level in Coronary Arteriosclerosis, Arch. Int. Med. **71**:397, 1943.
26. Morrison, L. M., Gonzales, W. T., and Hall, L.: The Significance of Cholesterol Variations in Human Blood Serum, J. Lab. & Clin. Med. **34**:1473, 1949.
27. Chandler, H. L., Lawry, E. A., Potee, K. A., and Mann, G. V.: Spontaneous and Induced Variations in Serum Lipoproteins, Circulation **8**:723, 1953.
28. Gertler, M. M., Garn, S. M., and Bland, E. F.: Age, Serum Cholesterol and Coronary Artery Disease, Circulation **2**:517, 1950.
29. Davis, D., Stearn, B., and Lesnich, G.: The Lipid and Cholesterol Content of the Blood of Patients With Angina Pectoris and Arteriosclerosis, Ann. Int. Med. **11**:354, 1937.
30. Lerman, J., and White, P. A.: Metabolic Changes in Young People With Coronary Heart Disease, J. Clin. Invest. **25**:914, 1946.
31. Morrison, L. M., Hall, L., and Chaney, A. L.: Cholesterol Metabolism: Blood Serum Cholesterol and Ester Levels in 200 Cases of Acute Coronary Thrombosis, Am. J. M. Sc. **216**:32, 1948.
32. Collen, M. F.: Blood Cholesterol Studies in Coronary Artery Disease, Permanente Foundation Med. Bull. **7**:55, 1949.
33. Gertler, M. M., Garn, S. M., and Lerman, J.: The Interrelationships of Serum Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease, Circulation **2**:205, 1950.
34. Steiner, A., Kendall, F. E., and Mathers, J. A. L.: The Abnormal Serum Lipid Pattern in Patients With Coronary Arteriosclerosis, Circulation **5**:605, 1952.
35. Oliver, M. F., and Boyd, G. S.: The Plasma Lipids in Coronary Artery Disease, Brit. Heart J. **15**:387, 1953.
36. Svendsen, M.: Are Supernormal Cholesterol-Values in Serum Caused by a Dominantly Inherited Factor? Acta med. scandinav. **104**:235, 1940.
37. Müller, C.: Xanthomata, Hypercholesterolemia, Angina Pectoris, Acta med. scandinav. Supp., **89**:75, 1938.
38. Müller, C.: Angina Pectoris in Hereditary Xanthomatosis, Arch. Int. Med. **64**:675, 1939.
39. Newman, B. A.: Xanthomatosis With Disease of the Coronary Arteries, Arch. Dermat. and Syph. **45**:198, 1942.
40. Engelberg, H., and Newman, B. A.: Xanthomatosis: A Cause of Coronary Artery Disease in Young Adults, J.A.M.A. **122**:1167, 1943.
41. Boas, E. P., and Adlersberg, D.: Familial Hypercholesterolemia (Xanthomatosis) and Atherosclerosis, J. Mt. Sinai Hosp. **12**:84, 1945.
42. Boas, E. P., Parets, A. D., and Adlersberg, D.: Hereditary Disturbance of Cholesterol Metabolism: A Factor in the Genesis of Atherosclerosis, Am. Heart J. **35**:611. 1948.
43. Wilkinson, C. F., Hand, E. A., and Fliegelman, M. T.: Essential Familial Hypercholesterolemia, Ann. Int. Med. **29**:671, 1948.
44. Adlersberg, D., Parets, A. D., and Boas, E. P.: Genetics of Atherosclerosis. Studies of Families With Xanthoma and Unselected Patients With Coronary Artery Disease Under the Age of Fifty Years. J.A.M.A. **141**:246, 1949.
45. Thomas, C. B.: Observations on Some Possible Precursors of Essential Hypertension and Coronary Artery Disease: V. Hypercholesteremia in Healthy Young Adults. Am. J. M. Sc. **232**:389, 1956.

46. Sackett, G. E.: Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum. J. Biol. Chem. **64**:203, 1925.
47. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., Nichols, A. V.: Lipoproteins in Atherosclerosis. Am. J. Med. **11**:358, 1951.
48. Sperry, W. M., and Webb, M.: The Effect of Increasing Age on Serum Cholesterol Concentration. J. Biol. Chem. **187**:107, 1950.
49. Man, E. B., and Peters, J. P.: Variations of Serum Lipids With Age, J. Lab. & Clin. Med. **41**:738, 1953.
50. Snedecor, G.: Statistical Methods, ed. 4, Ames, Iowa, The Collegiate Press, Inc., pp. 138-155.
51. Gofman, J. W., Jones, H. B., Thomas, P. L., Lindgren, F., Strisower, B., Colman, D., and Herring, V.: Blood Lipids and Human Atherosclerosis, Circulation **5**:119, 1952.
52. Keys, A.: The Physiology of the Individual as an Approach to a More Quantitative Biology of Man, Fed. Proc. **8**:523, 1949.
53. Page, I. H., Lewis, L. A., and Gilbert, J.: Plasma Lipids and Proteins and Their Relationship to Coronary Disease Among Navajo Indians, Circulation **13**:5, 1956.
54. Gildea, E. F., Kahn, E., and Man, E. B.: The Relationship Between Body Build and Serum Lipoids and a Discussion of These Qualities as Pyknophilic and Leptophilic Factors in the Structure of the Personality, Am. J. Psychiat. **92**:1247, 1935-36.
55. Walker, W. J.: Relationship of Adiposity to Serum Cholesterol and Lipoprotein Levels and Their Modification by Dietary Means, Ann. Int. Med. **39**:705, 1953.
56. Walker, A. R. P., and Arvidsson, U. B.: Fat Intake, Serum Cholesterol Concentration and Atherosclerosis in South African Bantu: I. Low Fat Intake and the Age Trend of Serum Cholesterol Concentration in South African Bantu. J. Clin. Invest. **33**:1358, 1954.
57. Higginson, J., and Pepler, W. J.: Fat Intake, Serum Cholesterol Concentration, and Atherosclerosis in the South African Bantu. Part II. Atherosclerosis and Coronary Artery Disease, J. Clin. Invest. **33**:1366, 1954.
58. Keys, A., Anderson, J. T., Fidanza, F., Keys, M. H., and Swahn, B.: Effects of Diet of Blood Lipids in Man; Particularly Cholesterol and Lipoproteins, Clin. Chem. **1**:34, 1955.
59. Keys, A.: The Diet and Development of Coronary Heart Disease. J. CHRON. DIS. **4**:364, 1956.
60. Groen, J., Tjiong, B. K., Kamminga, C. E., and Willebrands, A. F.: The Influence of Nutrition, Individuality, and Some Other Factors, Including Various Forms of Stress, on the Serum Cholesterol; and Experiment of Nine Months Duration in 60 Normal Human Volunteers, Voeding **13**:556, 1952.
61. Mann, G. V., and White, H. S.: The Influence of Stress on Plasma Cholesterol Levels, Metabolism **2**:47, 1953.
62. Groover, M. E.: Personal communication.

SERUM LIPOPROTEINS IN PRECLINICAL AND IN MANIFEST ISCHEMIC HEART DISEASE

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INTRODUCTION

AUTOPSY findings suggest that almost all North American men have at least some artherosclerosis of their coronary arteries.[1,2] Myocardial ischemia is the common sequel of coronary atherosclerosis and produces physiologic and/or pathologic changes which result in abnormal clinical symptoms and/or signs. It is the leading cause of death in the United States.[3,4] Cholesterol is the chief constituent of the atheromatous plaque. Since individuals suffering from ischemic heart disease often, but by no means invariably, have elevated blood levels of cholesterol, it is generally supposed that atherosclerosis may be a disorder of fat metabolism.[5,6] Numerous attempts have, therefore, been made to identify the individual already afflicted with, or destined to develop, ischemic heart disease by more or less elaborate characterization of the blood lipids.[7-11] The reported success of these efforts has varied considerably. The present study was designed to put several of these methods to the most rigorous test possible, that is, their ability to discriminate between the healthy and the diseased members of a group of middle-aged men comparable save for the presence or the presumed absence of ischemic heart disease.

1. *Clinical.*—One hundred and fifteen white men, with four exceptions, between the ages of 40 and 55 years, and of comparable racial, economic, and occupational status were surveyed. These men are participants in a prospective study of the evolution of degenerative heart disease. The design and methods of this study have been reported elsewhere.[12] A comprehensive clinical inventory, including, unless contraindicated, the electrocardiographic and ballistocardiographic responses to a standard exercise test, was repeated on each individual for the purpose of this study. Forty of the subjects were regarded as normal on the basis of this evaluation. Twenty-seven men, although apparently free of ischemic heart disease, showed features often regarded as predisposing to coronary atherosclerosis, such as obesity, hypertension, diabetes mellitus, or poor cardiovascular heredity. Twenty men had angina pectoris without historical or electrocardiographic evidence of previous myocardial infarction. Twenty-eight men

had survived a well-authenticated myocardial infarction. The men with ischemic heart disease were all working regularly and were only slightly or moderately disabled.

2. *Chemical.*—The subjects were bled after an overnight fast. Serum was used for all chemical analyses.

On the day of bleeding the serum β-lipoproteins were separated from the α-lipoproteins by Cohn's Method 10, using the procedure of Lever and his associates with minor modifications.[13,14] Tests by agar gel diffusion with antiserum to low-density lipoproteins indicated that Fraction IV + V contained no β-lipoprotein.[15]

The total cholesterol contents of the sera and of the Cohn fractions were determined by the method of Abell, Levy, Brodie, and Kendall.[16]

The lipid phosphorus contents of the sera and of the Cohn fractions were determined by a modification of the method of Fiske and Subbarow on aliquots of Bloor extracts of the serum and of the Cohn fractions. A factor of 25 was used to convert lipid phosphorus to phospholipids.[17]

The total lipid level of the serum and the lipid content of the Cohn fractions were measured by the dichromatesulfuric acid oxidation method of Bragdon.[18]

The flotation characteristics of the serum lipoproteins were measured at a solvent density of 1.21 by a modification of the method of Green, Lewis, and Page.[19]

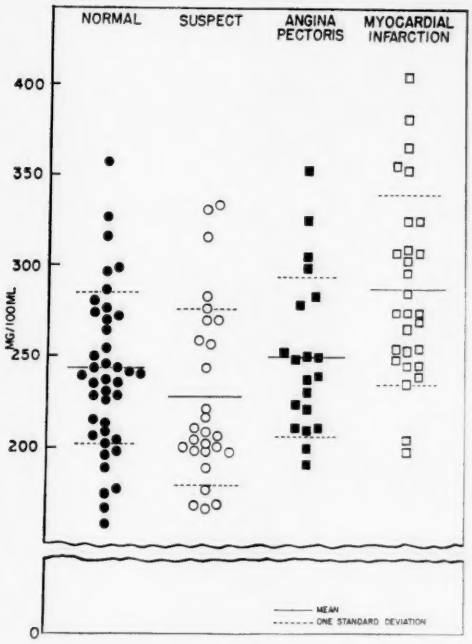
RESULTS

Tables I to V summarize by clinical category the ranges and the mean levels of the values for the various lipids measured. The raw data on which these summaries are based appear in Tables IA to IVA in the Appendix. Figs. 1 to 6 illustrate the total and fractional cholesterol and phospholipid values by clinical category.

TABLE I. AVERAGE SERUM LIPOPROTEIN-CHOLESTEROL (MG./100 ML.)

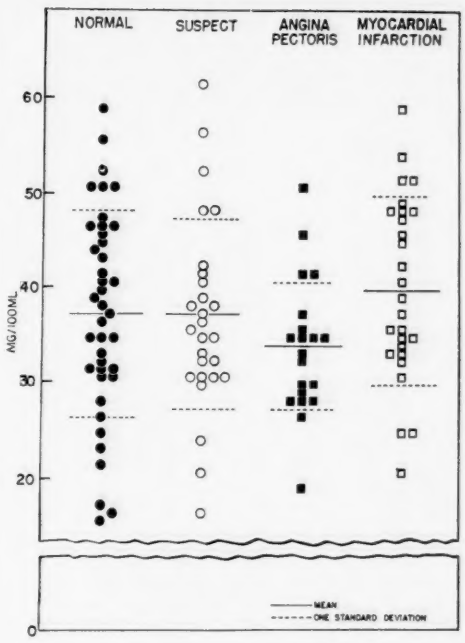
		TOTAL	ALPHA	BETA	PER CENT BETA
Normal	Mean ± SD	244 ± 41	37 ± 11	194 ± 44	84 ± 6
	Range	159 – 358	14 – 59	113 – 330	72 – 94
Suspect	Mean ± SD	229 ± 48	37 ± 10	186 ± 47	83 ± 6
	Range	168 – 333	15 – 62	118 – 282	68 – 93
Angina Pectoris	Mean ± SD	251 ± 44	33 ± 7	213 ± 42	86 ± 5
	Range	192 – 352	17 – 50	165 – 305	78 – 93
Myocardial Infarction	Mean ± SD	288 ± 51	39 ± 10	238 ± 51	86 ± 4
	Range	199 – 405	19 – 59	137 – 352	73 – 92

The serum total cholesterol level was significantly increased in the healed myocardial infarction group ($p < 0.01$) (Table I and Figs. 1, 2, and 3). This increase was accounted for by increases in the β-lipoprotein-cholesterol levels. The



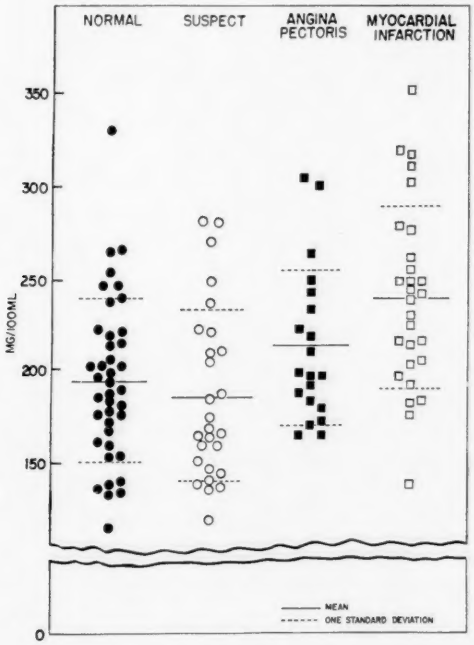
SERUM TOTAL CHOLESTEROL

Fig. 1.—Serum total cholesterol.



SERUM α LIPOPROTEIN CHOLESTEROL

Fig. 2.—Serum alpha lipoprotein cholesterol.



SERUM β LIPOPROTEIN CHOLESTEROL

Fig. 3.—Serum beta lipoprotein cholesterol.

TABLE II. AVERAGE SERUM LIPOPROTEIN-PHOSPHOLIPID (MG./100 ML.)

		TOTAL	ALPHA	BETA	PER CENT BETA
Normal	Mean ± SD	270 ± 44	93 ± 19	171 ± 43	64 ± 8
	Range	186 – 378	65 – 131	110 – 308	47 – 82
Suspect	Mean ± SD	273 ± 45	91 ± 22	176 ± 48	65 ± 11
	Range	187 – 349	35 – 140	86 – 275	49 – 85
Angina Pectoris	Mean ± SD	275 ± 33	83 ± 13	189 ± 33	69 ± 5
	Range	222 – 350	63 – 116	144 – 258	59 – 77
Myocardial Infarction	Mean ± SD	318 ± 39	98 ± 21	214 ± 43	68 ± 8
	Range	235 – 384	56 – 136	140 – 282	52 – 80

TABLE III. AVERAGE SERUM LIPOPROTEIN-CHOLESTEROL: PHOSPHOLIPID RATIOS

		TOTAL	ALPHA	BETA
Normal	Mean ± SD	.90 ± .08	.39 ± .10	1.15 ± .18
	Range	.71 – 1.32	.15 – .62	.85 – 1.74
Suspect	Mean ± SD	.84 ± .11	.39 ± .08	1.07 ± .15
	Range	.64 – 1.12	.31 – .55	.79 – 1.37
Angina Pectoris	Mean ± SD	.92 ± .11	.39 ± .05	1.12 ± .07
	Range	.73 – 1.01	.28 – .48	.94 – 1.26
Myocardial Infarction	Mean ± SD	.91 ± .07	.40 ± .03	1.12 ± .15
	Range	.71 – 1.10	.27 – .50	.77 – 1.37

α-lipoprotein-cholesterol levels were the same in all groups. The percentage distribution of cholesterol between the two lipoprotein fractions was the same in all groups since the increases in the total and in the β-lipoprotein-cholesterol were of the same relative magnitude.

The serum total phospholipid and the serum α- and β-lipoprotein-phospholipid levels displayed precisely the pattern described for cholesterol (Table II and Figs. 4, 5, and 6). The cholesterol: phospholipid ratios were identical in both the presumably healthy and diseased individuals (Table III).

The serum total lipids (Table V) and the α- and β-lipoprotein-lipids were essentially the same in all 4 categories.

Finally, the $-S_{1.21}10+$ flotation classes showed increases in the mean values in the healed myocardial infarction group as compared with the normal individuals ($p < 0.05$) (Table IV) (see Appendix Tables IA to IVA).

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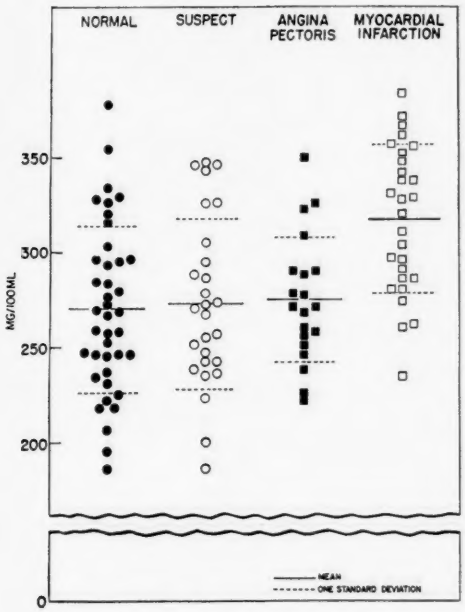

Fig. 4.—Serum total phospholipid.

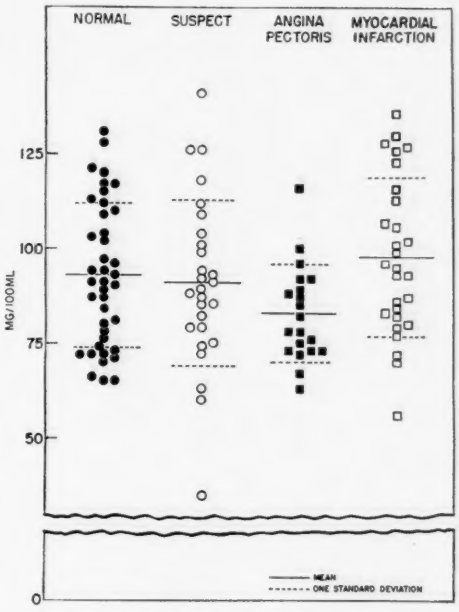

Fig. 5.—Serum alpha lipoprotein phospholipid.

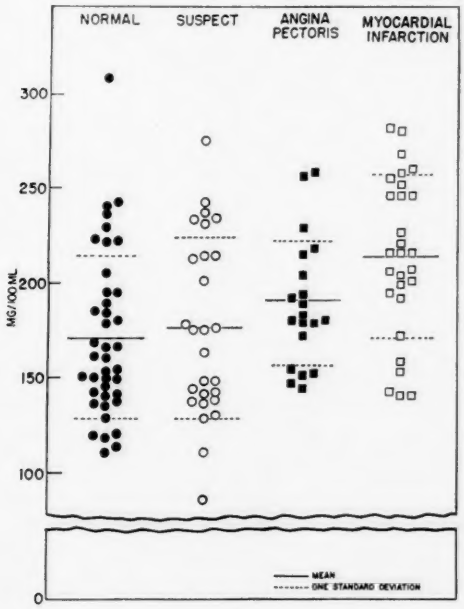

Fig. 6.—Serum beta lipoprotein phospholipid.

TABLE IV. AVERAGE ULTRACENTRIFUGAL LIPOPROTEIN CONCENTRATION (MG./100 ML.)

		$-S_{1.21}1\text{-}10$	$-S_{1.21}10\text{-}52$	$-S_{1.21}52\text{-}74$	$-S_{1.21}74\text{-}300$	$-S_{1.21}300\text{-}500$
Normal	Mean ± SD	85 ± 27	238 ± 59	22 ± 16	56 ± 39	35 ± 41
	Range	27 – 137	84 – 396	0 – 93	0 – 184	0 – 178
Suspect	Mean ± SD	87 ± 35	240 ± 77	22 ± 11	58 ± 29	65 ± 60
	Range	41 – 213	54 – 395	9 – 60	17 – 151	2 – 210
Angina Pectoris	Mean ± SD	72 ± 24	301 ± 64	29 ± 12	67 ± 25	55 ± 46
	Range	28 – 108	193 – 427	6 – 60	26 – 137	7 – 191
Myocardial Infarction	Mean ± SD	90 ± 28	285 ± 70	31 ± 17	80 ± 41	68 ± 72
	Range	42 – 167	144 – 468	10 – 100	29 – 220	8 – 337

TABLE V. AVERAGE TOTAL LIPID (MG. $K_2Cr_2O_7$ RED./100 ML.)

		TOTAL	ALPHA	BETA
Normal	Mean ± SD	12530 ± 2861	2920 ± 1221	9224 ± 2615
	Range	8210 – 20250	1734 – 9590	5720 – 16320
Suspect	Mean ± SD	12118 ± 2928	2692 ± 1165	9015 ± 3223
	Range	6525 – 20000	1155 – 8060	3915 – 15720
Angina Pectoris	Mean ± SD	12890 ± 1836	2337 ± 414	9833 ± 2083
	Range	10268 – 17080	1751 – 3460	7242 – 14920
Myocardial Infarction	Mean ± SD	13849 ± 3189	2605 ± 440	10763 ± 3173
	Range	8704 – 22300	1623 – 3690	6560 – 20400

DISCUSSION

The present study emphasizes certain biochemical similarities of a group of apparently healthy middle-aged men and a comparable age group characterized with the diagnosis of myocardial ischemia. As a group, the survivors of myocardial infarction showed significant elevations of the total lipoprotein-cholesterol and -phospholipid and of the $-S_{1.21}10+$ groups. The large overlap of values, however, vitiated the discriminatory value of the individual observation. Although we found substantial increases in the β-lipoprotein-cholesterol in the survivors of myocardial infarction, we were unable to demonstrate the reciprocal decrease in α-lipoprotein-cholesterol described by others.[8,10] This discrepancy is not explained by our use of serum in preference to plasma. A systematic comparison of serum with plasma revealed similar recoveries of total and of β-lipoprotein-cholesterol and -phospholipid and, on the average, 11 per cent and 7 per cent

higher values, respectively, for α-lipoprotein-cholesterol and -phospholipid in plasma. We are unable to account for the unexpected observation that individuals with angina pectoris showed lipid patterns resembling those of normal individuals rather than those of survivors of myocardial infarction. Actuarially damaging features such as hypertension and obesity showed no correlation with the chemical findings. In common with others, our experience with the ultracentrifugal characterization of serum lipoproteins leaves us skeptical of the sensitivity, accuracy, or reproducibility of the procedure.[20]

SUMMARY

1. Of 115 middle-aged, white, male office workers, 76 were considered clinically free of ischemic heart disease, although 27 were obese, hypertensive, diabetic, or had a strong family history of heart disease. Of the remaining 48 men, 28 had survived a myocardial infarction and 20 had only angina pectoris.

2. The survivors of myocardial infarction as a group showed significant increases in the lipoprotein-cholesterol and -phospholipid which were accounted for by increases in the β-lipoprotein fractions; there were also significant increases in the $-S_{1.21}$ flotation fractions above $-S_{1.21}1\text{-}10$. The wide overlap of values in all groups nullified the individual diagnostic value of the measurements.

3. The presently available techniques for measuring the blood lipoproteins are neither qualitatively nor quantitatively satisfactory indices of atherogenicity in a homogeneous population highly susceptible to ischemic heart disease.

CONCLUSION

The presently available methods for quantitating the blood lipoproteins do not discriminate between the individual members of a homogeneous population universally predisposed to coronary atherosclerosis and differing only in the presence or absence of complicating myocardial ischemia. A matter of practical importance is that the serum total cholesterol provides as much (or as little) information as other more elaborate and difficult chemical procedures. It is possible that serial observations of such a population may provide more valuable information.

APPENDIX

(Tables IA-IVA Follow.)

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TABLE IA

UNIT NO.	AGE	SERUM CHOLESTEROL (MG./100 ML.)				SERUM PHOSPHOLIPID (MG./100 ML.)				CHOLESTEROL: PHOSPHOLIPID			ULTRACENTRIFUGAL LIPOPROTEIN CONCENTRATION (MG./100 ML.)					TOTAL LIPID (MG. $K_2Cr_2O_7$ RED./100 ML.)		
NORMAL		TOTAL	α	β	%β	TOTAL	α	β	%β	TOTAL	α	β	$-S_{1\cdot21}$1-10	$-S_{1\cdot21}$10-52	$-S_{1\cdot21}$52-74	$-S_{1\cdot21}$74-300	$-S_{1\cdot21}$300-500	TOTAL	α	β
1532	48	159	40	113	74	206	80	110	58	.77	.50	1.03	54	164	12	58	90	8210	2305	6090
89	43	168	16	132	89	237	102	135	57	.71	.16	.98	82	159	9	—	—	10385	3380	8020
384	44	175	31	135	82	195	72	128	64	.90	.43	1.05	59	191	13	38	4	8710	2110	6080
1600	46	178	30	140	82	218	71	141	67	.82	.42	.99	59	245	19	46	6	9250	2245	6090
240	42	190	46	133	74	246	117	120	51	.78	.39	1.11	116	169	2	23	22	10680	3620	6430
144	45	197	51	137	73	231	113	119	51	.85	.44	1.15	117	177	7	8	16	9520	3230	5780
232	47	199	14	153	92	266	94	169	64	.75	.15	.91	81	202	36	124	—	13240	3985	9480
699	47	203	37	172	82	225	87	137	61	.91	.43	1.25	64	250	19	17	13	10200	2720	7242
233	52	204	27	175	87	222	73	142	66	.92	.37	1.24	72	257	27	67	34	10400	2010	7350
197	49	207	41	161	80	234	90	136	60	.88	.45	1.18	50	121	4	24	6	11630	2995	8738
337	44	209	34	167	83	252	91	153	63	.83	.37	1.09	63	216	18	36	48	11520	2730	8720
1904	49	213	59	153	72	259	128	113	47	.82	.46	1.35	126	240	24	19	4	9930	3060	5720
982	49	215	30	190	87	218	70	145	67	.99	.43	1.31	40	261	5	28	13	9310	2023	7310
911	55	226	34	178	84	245	81	150	65	.92	.42	1.18	73	211	7	29	8	11550	2490	8010
569	40	228	44	175	80	246	97	149	61	.93	.46	1.18	113	84	6	12	5	10250	3330	6700
256	45	228	37	187	84	246	87	161	65	.93	.42	1.16	78	203	93	184	45	10880	2345	8090
308	46	231	36	180	83	258	93	154	62	.90	.38	1.17	86	223	17	39	11	9730	2585	7410
114	44	234	23	196	89	272	65	189	74	.86	.37	1.04	86	227	35	82	68	15220	2210	11220
205	51	236	45	183	80	279	104	166	61	.85	.44	1.11	53	194	20	26	10	10930	2890	7480
1718	48	237	56	159	74	328	121	185	60	.72	.46	.85	116	225	20	48	141	14500	3135	9900
212	51	240	31	202	87	276	84	184	69	.87	.37	1.10	95	302	44	87	38	12510	2195	9420
83	48	241	31	201	87	247	74	179	71	.98	.41	1.12	62	192	15	44	26	11750	2160	8910

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63	45	242	47	194	80	284	110	166	60	.85	.43	1.17	95	220	28	43	12	14144	3400	8874
2087	44	244	46	198	81	257	103	150	59	.95	.44	1.32	92	247	22	59	7	10880	2312	8058
736	47	244	40	206	84	186	65	118	64	1.32	.62	1.74	92	316	—	39	17	10070	2175	7620
79	41	246	22	237	92	293	72	242	77	.84	.31	.98	50	263	34	149	—	16260	9590	13710
360	46	251	52	185	78	320	131	180	58	.78	.40	1.03	137	269	27	64	54	16250	4080	11560
188	48	255	44	213	83	316	115	195	63	.80	.37	1.09	124	224	23	67	62	14340	3280	10430
548	48	265	39	221	85	296	89	195	69	.90	.44	1.13	83	209	16	63	69	14930	2535	11490
143	44	270	51	201	80	269	109	149	58	1.00	.46	1.35	115	276	11	50	19	11500	3200	8200
333	42	272	25	240	90	303	72	222	76	.90	.35	1.08	27	245	31	86	93	16400	1940	13260
338	48	274	38	219	85	354	120	240	67	.78	.32	.91	89	253	42	130	88	20250	3950	14510
346	46	276	46	214	82	268	94	160	63	1.03	.49	1.34	110	320	12	40	7	12580	3025	8510
24	41	282	15	247	94	295	78	221	74	.95	.19	1.12	82	396	10	—	—	15520	3180	12970
2150	35	287	51	222	81	283	117	139	54	1.01	.44	1.59	121	264	14	42	6	10200	2875	7720
104	43	296	32	254	89	329	96	229	70	.90	.34	1.11	90	277	32	67	35	16380	2840	12530
309	44	303	31	247	89	326	91	236	72	.93	.35	1.05	111	304	31	96	107	17080	2345	13500
1687	53	317	34	266	89	296	76	205	73	1.06	.44	1.30	82	310	29	92	48	13100	2175	10200
566	45	327	43	265	86	334	112	223	67	.98	.38	1.18	114	316	25	32	7	12784	2414	9316
1064	44	358	20	330	94	378	66	308	82	.94	.31	1.07	47	314	35	80	178	18224	1734	16320
Mean	46	244	37	194	84	270	93	171	64	.90	.39	1.15	85	238	22	56	35	12530	2920	9224
Range																				
From	35	159	14	113	72	186	65	110	47	.71	.15	.85	27	84	0	0	0	8210	1734	5720
To	55	358	59	330	94	378	131	308	82	1.32	.62	1.74	137	396	93	184	178	20250	9590	16320
S. D.	± 4	± 41	± 11	± 44	± 6	± 44	± 19	± 43	± 8	± .08	± .10	± .18	± 27	± 59	± 16	± 39	± 41	± 2861	± 1221	± 2615

TABLE IIA

UNIT NO. SUSPECT	AGE	CLINICAL* STATUS	SERUM CHOLESTEROL (MG./100 ML.)				SERUM PHOSPHOLIPID (MG./100 ML.)				CHOLESTEROL: PHOSPHOLIPID			ULTRACENTRIFUGAL LIPOPROTEIN CONCENTRATION (MG./100 ML.)					TOTAL LIPID (MG. $K_2Cr_2O_7$ RED./100 ML.)		
			TOTAL	α	β	%β	TOTAL	α	β	%β	TOTAL	α	β	$S_{f\ 1.21}$1-10	$S_{f\ 1.21}$10-52	$S_{f\ 1.21}$52-74	$S_{f\ 1.21}$74-300	$S_{f\ 1.21}$300-500	TOTAL	α	β
943	44	P.; 1 Sib.	168	48	118	71	187	89	86	49	.90	.54	1.37	77	192	9	41	2	6525	2485	3915
1560	51	H.D.	169	19	144	88	242	60	176	75	.70	.32	.82	41	224	17	82	157	9320	1787	7250
387	46	E.O.	170	31	136	81	200	74	128	63	.85	.43	1.06	70	232	14	29	23	9248	2176	6158
1714	46	E.O.	178	38	140	78	247	104	142	58	.72	.37	.98	119	246	27	70	84	11100	2720	8160
298	52	E.O.	190	37	146	80	272	118	148	57	.70	.31	.98	104	54	18	33	40	11290	2880	8200
438	42	?ECG	198	30	164	85	223	79	138	64	.89	.37	1.18	70	214	17	31	42	9316	2193	6936
577	61	H.D.; P	199	41	150	79	255	109	141	56	.78	.37	1.06	72	144	16	55	32	10948	2771	7820
530	52	H.D.	200	57	138	71	286	140	136	49	.70	.40	1.01	121	130	16	53	21	10336	3417	6460
627	46	H.D.; P	201	35	168	83	242	88	148	63	.83	.39	1.13	66	148	14	31	13	12300	2840	8364
172	46	E.O.	201	36	166	82	278	99	175	64	.72	.36	.95	104	230	26	62	92	13720	2790	9660
118	53	E.O.	202	29	160	85	236	75	137	65	.85	.38	1.17	67	216	18	47	19	11900	8060	2240
32	46	E.O.; LET	204	15	187	93	235	35	201	85	.87	.43	.92	71	203	30	56	71	11550	1155	10200
658	45	H.D.	208	42	163	80	251	94	145	61	.83	.44	1.12	76	212	10	30	28	9180	2665	6460
1538	55	D.M.	209	62	134	68	238	112	110	50	.87	.55	1.22	213	174	9	37	2	7350	3150	4360
189	41	H.D.	212	37	173	82	257	91	163	64	.93	.41	1.06	79	202	20	36	84	12790	2465	9280
684	48	D.M.	217	52	160	75	270	126	130	51	.80	.42	1.23	156	270	42	95	11	10200	3417	6562
107	51	H.D.; E.O.	221	30	184	86	343	93	231	71	.64	.32	.79	68	184	14	43	179	17000	2245	13610
1128	50	H.D.; E.O.	244	32	204	86	273	87	175	67	.90	.37	1.17	65	304	34	49	23	11428	2465	9214
518	52	H.D.	256	34	208	86	267	86	178	67	.96	.39	1.17	74	287	16	54	50	11400	2240	9110
901	51	H.D.	259	31	221	88	326	82	237	74	.79	.38	.93	78	252	17	81	141	20000	2550	15530
1450	42	H.D.	269	48	210	81	346	126	234	65	.78	.38	.90	119	395	20	57	202	15630	2670	12850
1747	47	H.D.	270	30	222	88	288	79	214	73	.94	.37	1.04	76	364	28	74	55	12300	1870	10200
513	48	D.M.	277	23	248	92	349	63	275	81	.79	.36	.90	55	320	39	151	210	15580	1836	15720
1232	50	H.D.	283	34	236	87	305	85	214	72	.92	.40	1.11	103	313	17	52	39	13050	2230	10480
768	41	H.D.; P	316	40	270	87	326	92	242	72	.97	.44	1.12	47	332	31	71	84	13872	2210	11628
226	47	E.O.	330	37	282	88	346	101	233	70	.96	.37	1.21	91	364	60	120	38	15504	3128	12206
159	42	?CI; P	333	30	282	90	295	72	211	75	1.12	.41	1.33	74	268	14	17	12	14340	2260	10840
Mean	48		229	37	186	83	273	91	176	65	.84	.39	1.07	87	240	22	58	65	12118	2692	9015
Range																					
From	41		168	15	118	68	187	35	86	49	.64	.31	.79	41	54	9	17	2	6525	1155	3915
To	61		333	62	282	93	349	140	275	85	1.12	.55	1.37	213	395	60	151	210	20000	8060	15720
S. D.	±4		± 48	±10	± 47	±6	±45	±22	±48	±11	± .11	± .08	± .15	±35	±77	±11	±29	±60	±2928	±1165	±3223

*H.D. = hypertensive disease; E.O. = obesity; ?ECG = borderline ECG response; P = parent; LET = limited exercise tolerance; D.M. = diabetes mellitus, treated; ?CI = possible coronary insufficiency.

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TABLE IIIA

UNIT NO. ANGINA PECTORIS	AGE	CLINICAL STATUS (YEARS)	SERUM CHOLESTEROL (MG./100 ML.)				SERUM PHOSPHOLIPID (MG./100 ML.)				CHOLESTEROL: PHOSPHOLIPID			ULTRACENTRIFUGAL LIPOPROTEIN CONCENTRATION (MG./100 ML.)					TOTAL LIPID (MG. $K_2Cr_2O_7$ RED./100 ML.)		
			TOTAL	α	β	%β	TOTAL	α	β	%β	TOTAL	α	β	—$S_{1.21}$1-10	—$S_{1.21}$10-52	—$S_{1.21}$52-74	—$S_{1.21}$74-300	—$S_{1.21}$300-500	TOTAL	α	β
2105	65	AP; ½	192	29	165	85	222	73	147	67	.86	.39	1.12	70	226	17	66	46	10268	1751	7242
793	52	AP; 3	201	27	172	86	226	72	152	68	.89	.37	1.13	77	266	21	55	23	11020	2345	8500
451	52	AP; 3	210	45	165	78	246	100	144	59	.85	.45	1.14	108	193	6	26	7	11080	2380	8770
1939	61	AP; 2	212	37	170	82	251	92	154	63	.84	.40	1.11	93	298	26	66	16	12630	3460	8300
263	54	AP; 2	212	25	192	88	291	87	204	70	.73	.29	.94	34	225	44	73	142	15300	1955	12640
1245	41	AP; 1	221	34	183	84	278	89	179	67	.79	.38	1.02	77	354	29	54	17	12200	2580	8850
540	50	AP; 5	225	34	187	85	260	88	180	67	.86	.38	1.04	96	298	35	51	56	12300	2685	8510
56	49	AP; 4	230	41	180	81	256	96	151	61	.90	.43	1.19	102	276	20	35	11	11968	2941	7650
330	53	AP; 2	238	27	197	88	258	73	183	71	.92	.37	1.07	73	363	34	64	8	13460	2210	10270
910	52	AP; 5	240	32	196	86	238	67	172	72	1.01	.48	1.14	33	251	26	137	90	10670	2415	7825
1142	52	AP; 3	249	35	210	86	271	76	194	72	.92	.46	1.08	94	230	35	56	92	14220	2230	10600
1197	52	AP; 3	249	31	199	86	268	78	179	70	.93	.40	1.11	67	370	26	61	68	11696	2006	8806
1281	50	AP; 2	250	34	222	87	271	82	180	69	.92	.42	1.24	75	403	39	54	66	10540	1768	8430
1746	46	AP; 2	253	17	219	93	291	63	215	77	.87	.28	1.02	28	375	29	83	51	13100	2040	11050
1275	54	AP; 1	278	41	234	85	277	92	189	67	1.00	.44	1.24	99	322	30	70	64	11010	1921	7888
15	55	AP; ½	282	28	249	90	288	73	218	75	.98	.38	1.14	48	235	41	104	62	14400	2400	12200
824	55	AP; 1	298	50	243	83	309	116	192	62	.97	.44	1.26	89	299	16	30	24	12920	2940	9180
261	51	AP; 1	305	29	264	90	326	78	229	75	.93	.37	1.15	63	295	28	87	38	16520	2330	12630
1740	47	AP; 1	324	27	300	92	323	75	256	77	1.00	.36	1.17	45	319	19	68	191	17080	2225	14920
1522	50	AP; 3	352	34	305	90	350	85	258	75	1.00	.40	1.19	65	427	60	98	26	15700	2160	12400
Mean	52		251	33	213	86	275	83	189	69	.92	.39	1.12	72	301	29	67	55	12890	2337	9833
Range																					
From	41		192	17	165	78	222	63	144	59	.73	.28	.94	28	193	6	26	7	10268	1751	7242
To	65		352	50	305	93	350	116	258	77	1.01	.48	1.26	108	427	60	137	191	17080	3460	14920
S. D.	±5		± 44	± 7	± 42	±5	±33	±13	±33	±5	± .11	± .05	± .07	±24	±64	±12	±25	±46	±1836	±414	±2083

TABLE IVA

UNIT NO. MYOCARDIAL INFARCTION	AGE	CLINICAL STATUS	SERUM CHOLESTEROL (MG./100 ML.)				SERUM PHOSPHOLIPID (MG./100 ML.)				CHOLESTEROL: PHOSPHOLIPID			ULTRACENTRIFUGAL LIPOPROTEIN CONCENTRATION (MG./100 ML.)					TOTAL LIPID (MG. $K_2Cr_2O_7$ RED./100 ML.)		
			TOTAL	α	β	α/β	TOTAL	α	β	α/β	TOTAL	α		$S_{1.21}$1-10	$S_{1.21}$10-52	$S_{1.21}$52-74	$S_{1.21}$74-300	$S_{1.21}$300-500	TOTAL	α	β
246	50	MI; 4 yr.	199	51	137	73	280	123	140	53	.71	.42	.98	126	171	19	65	97	14100	3690	8560
1283	48	MI; 1 yr.	205	32	175	84	235	80	153	66	.87	.40	1.14	80	306	29	69	32	8704	2040	6595
639	47	MI; 2 yr.	236	31	195	86	274	88	192	69	.86	.36	1.02	89	240	35	73	70	13600	2685	11240
721	45	MI; 6 mo.	240	49	183	79	286	126	158	56	.84	.38	1.16	101	284	26	58	8	9996	2737	7072
1782	50	MI; 1 yr.	245	54	182	77	286	130	142	52	.85	.42	1.28	98	238	28	49	48	12100	3025	7825
177	45	MI; 3 yr.	246	35	202	85	261	95	172	64	.94	.37	1.18	82	237	29	49	10	12170	2860	8850
52	53	MI; 2 yr.	249	19	214	92	329	72	258	78	.76	.27	.83	42	144	29	103	337	22300	2125	20400
1743	51	MI; 10 yr.	254	33	224	87	304	84	204	71	.84	.39	1.10	54	292	24	67	61	13300	2423	10055
1574	55	MI; 10 yr.	255	51	192	79	262	102	140	58	.97	.50	1.37	88	245	15	34	13	9790	2760	6560
789	54	MI; 6 mo.	255	30	205	87	297	83	206	71	.85	.36	.99	86	270	49	99	70	13500	2240	9760
1402	45	MI; 3 yr.	266	37	216	86	291	101	199	66	.92	.37	1.09	108	202	36	51	17	13180	2890	9900
1508	54	MI; 5 yr.	269	32	230	88	320	79	227	74	.85	.41	1.01	115	468	40	107	94	15350	2600	12400
805	46	MI; 2 yr.	274	45	216	83	331	116	282	71	.83	.39	.77	122	249	20	70	69	10470	2905	8710
884	44	MI; 6 mo.	275	24	255	92	340	70	255	78	.81	.34	1.00	70	337	100	220	224	17500	2040	15300
1284	45	MI; 4 yr.	275	24	242	91	280	56	221	80	.99	.42	1.02	63	403	27	68	81	12380	1623	10680
242	55	MI; 3 yr.	286	47	239	84	384	127	246	66	.74	.37	.97	167	251	28	104	102	16910	3350	13320
1255	48	MI; 1 yr.	296	38	249	87	311	86	216	72	.95	.44	1.15	58	342	27	52	38	12430	2790	8975
1523	53	MI; 2 yr.	303	34	249	88	296	77	195	72	1.03	.44	1.28	65	210	13	29	15	10860	2005	8865
2008	40	MI; 4 yr.	307	59	248	81	362	136	201	60	.85	.44	1.24	94	288	10	110	13	11420	3130	7690
1332	55	MI; 6 yr.	307	48	244	84	348	128	207	62	.88	.37	1.18	130	248	17	41	38	13270	3120	9620
845	51	MI; 1 mo.	309	42	262	86	328	107	216	67	.94	.39	1.21	86	327	22	76	36	12920	2482	9928
891	52	MI; 2 yr.	324	35	279	89	372	93	281	75	.87	.37	.99	78	294	35	163	184	22200	2520	17690
8	42	MI; 5 mo.	324	48	276	85	338	113	221	66	.96	.43	1.25	86	256	38	137	19	12280	2774	9445
1794	50	MI; 9 yr.	352	37	311	89	356	96	260	73	.99	.38	1.19	88	380	50	107	82	16450	2380	13250
1161	46	MI; 2 yr.	355	44	303	87	357	93	252	73	.99	.48	1.20	115	374	47	82	65	16200	2550	12500
1515	52	MI; 4 yr.	365	40	318	89	343	99	246	71	1.06	.40	1.29	126	348	24	58	48	15096	2618	12138
1014	54	MI; 1½ yr.	382	48	320	87	352	106	246	70	1.08	.45	1.30	54	328	17	69	10	13100	2345	10530
11	44	MI; 6 mo.	405	34	352	91	367	82	268	77	1.10	.42	1.32	62	262	30	42	30	16184	2244	13520
Mean	49		288	39	238	86	318	98	214	68	.91	.40	1.12	90	285	31	80	68	13849	2605	10763
Range																					
From	40		199	19	137	73	235	56	140	52	.71	.27	.77	42	144	10	29	8	8704	1623	6560
To	55		405	59	352	92	384	136	282	80	1.10	.50	1.37	167	468	100	220	337	22300	3690	20400
S. D.	±5		±51	±10	±51	±4	±39	±21	±43	±8	± .07	± .03	± .15	±28	±70	±17	±41	±72	±3189	±440	±3173

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REFERENCES

1. White, N. K., Edwards, J. E., and Dry, T. D.: The Relationship of the Degree of Coronary Artherosclerosis With Age in Men, Circulation **1**:645, 1950.
2. Enos, W. F., Holmes, R. H., and Bayer, J.: Coronary Disease Among United States Soldiers Killed in Action in Korea, J.A.M.A. **152**:1090, 1953.
3. Gould, S. E.: Pathology of the Heart, Springfield, Ill., 1953, Charles C Thomas, pp. 548-637.
4a. Vital Statistics of the United States, 1952, Volume II. U. S. Dept. of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics. Washington, D. C., 1955, U. S. Government Printing Office.
4b. Mortality from Selected Causes by Age and Sex: United States, 1953. Vital Stat. Spec. Reports, Sept. 12, 1955, Vol. 42, No. 7. U. S. Dept. of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics, Washington, D. C.
5. Katz, L. N., and Stamler, J.: Experimental Atherosclerosis. Springfield, Ill., 1953, Charles C Thomas.
6. Symposium on Atherosclerosis, National Research Council Publication 338, Washington, D. C., 1954.
7. Keys, A.: "Giant Molecules" and Cholesterol in Relation to Atherosclerosis, Bull. Johns Hopkins Hosp. **88**:473, 1951.
8a. Russ, E. M., Eder, H. A., and Barr, D. P.: Protein-lipid Relationships in Human Plasma. I. In Normal Individuals, Am. J. Med. **11**:468, 1951.
8b. Barr, D. P., Russ, E. M., and Eder, H. A.: Protein-lipid Relationships in Human Plasma. II. In Atherosclerosis and Related Conditions, Am. J. Med. **11**:480, 1951.
9. Gertler, M. M., and White, P. D.: Coronary Artery Disease in Young Adults. Cambridge, 1954, Harvard University Press.
10. Oliver, M. F., and Boyd, G. S.: Serum Lipoprotein Patterns in Coronary Sclerosis and Associated Conditions, Brit. Heart J. **17**:299, 1955.
11. Gofman, J. W., Hanig, M., Jones, H. B., Lauffer, M. A., Lawry, E. Y., Lewis, L. A., Mann, G. V., Moore, F. E., Olmsted, F., and Yeager, J. F.: Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis, Circulation **14**:691, 1956.
12. Hilleboe, H. E., James, G., and Doyle, J. T.: Cardiovascular Health Center. I. Project Design for Public Health Research, Am. J. Pub. Health, **44**:851, 1954.
13. Cohn, E. J., Gurd, F. R. N., Surgenor, D. M., Barnes, B. A., Brown, R. K., Derouaux, G., Gillespie, J. M., Kahnt, F. W., Lever, W. F., Liu, C. H., Mittleman, D., Moutin, R. F., Schmid, K., and Uroma, E.: A System for the Separation of the Components of Human Blood: Quantitative Procedures for the Separation of the Protein Components of Human Plasma, J. Am. Chem. Soc. **72**:465, 1950.
14. Lever, W. F., Gurd, F. R. N., Uroma, E., Brown, R. K., Barnes, B. A., Schmid, K., and Shultz, E. L.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation. XI. Quantitative Separation and Determination of the Protein Components in Small Amounts of Normal Human Plasma, J. Clin. Invest. **30**:99, 1951.
15. Ouchterlony, Ö.: Antigen-antibody Reactions in Gels. Types of Reactions in Coordinated Systems of Diffusion, Acta path. et microbiol. scandinav. **32**:231, 1953.
16. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A Simplified Method for the Estimation of Total Cholesterol in Serum and Demonstration of its Specificity, J. Biol. Chem. **195**:357, 1952.
17. Fiske, C. H., and Subbarow, Y., The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.
18. Bragdon, J. H., Colorimetric Determination of Blood Lipids, J. Biol. Chem. **190**:513, 1951.
19. Green, A. A., Lewis, L. A., and Page, I. H.: A Method For the Ultracentrifugal Analysis of α and Serum β Lipoproteins, Fed. Proc. **10**:191, 1951.
20. Watkin, D. M., Lawry, E. Y., Mann, G. V., and Halperin, M., A Study of Serum Beta Lipoprotein and Total Cholesterol Variability and its Relation to Age and Serum Level in Adult Human Subjects, J. Clin. Invest. **33**:874, 1954.

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Review

DRUG THERAPY FOR CHILDHOOD EPILEPSY

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THE purpose of this paper is to present the current status of drug therapy for childhood epilepsy, based on our experiences and those of others.

In discussing the efficacy of the various anticonvulsant drugs, it is necessary to present our classification of epileptic seizures, particularly our distinction between petit mal and minor motor spells, since many physicians designate all seizures of momentary duration as petit mal.

Epileptic seizures in children may manifest themselves in a variety of forms. While it is difficult to classify the attack in some instances, most seizures may be placed into four distinct types: major motor (grand mal), petit mal, minor motor, and psychomotor.

TYPES OF SEIZURES

A. *Major Motor (Grand Mal) Seizures.*—A major motor seizure may either be generalized or focal in its clinical manifestations. The salient feature of a generalized major motor seizure is a disturbance of consciousness which may be either complete or partial, depending upon the severity of the seizure. On the other hand, in most instances, there is no apparent impairment of consciousness associated with a focal major motor seizure. Tongue biting, urinary incontinence, and fecal incontinence do not occur as frequently in children with major seizures as in adults.

A major motor seizure may be of momentary duration or may last for several hours or longer. When the seizure is brief, the patient is usually able to resume activity within several minutes or so after the spell has subsided. However, at the end of a protracted seizure, the patient usually passes into a deep sleep or coma which persists for varying intervals of time. After recovering from this so-called postconvulsive sleep or coma, the patient generally manifests a variety of irregular and inconsistent signs or symptoms which are designated as postconvulsive phenomena.

Four distinct types of major motor seizures are encountered in children:

a. *Tonic-clonic type:* This is the most frequent type observed. During such an attack the patient, if standing, falls with board-like rigidity (tonic phase) in whatever direction he happens to be leaning. The tonic rigidity soon changes to very rapid generalized jerking moments (clonic phase).

b. *Tonic type:* During a spell of this type the patient becomes unconscious and his musculature remains in a tonic (board-like) state throughout the entire attack.

c. *Clonic type:* This type of spell begins with rapid jerking movements of the muscles which continue throughout the entire seizure.

d. *Atonic type:* During a spell of this kind the patient suddenly becomes limp and falls to the floor in an unconscious state. The musculature remains flaccid throughout the entire spell. There is no apparent tonic or clonic phase associated with such spells. This type of major motor seizure frequently is classified by others as drop or inhibitory seizures. It is also important that an akinetic minor motor seizure not be confused with an atonic major motor seizure. The main differences between these two types of attacks are as follows: an akinetic minor motor seizure is usually of very short duration, lasting several seconds or so and the return of complete consciousness is almost immediate; whereas, an atonic major motor seizure persists for at least several minutes or so and the return of consciousness is gradual.

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The interseizure electroencephalograms of patients with major motor epilepsy show a variety of findings. Normal tracings, abnormally slow waves, abnormally fast waves, spikes, sharp waves, and spike and wave forms other than the classical three per second spike and wave form of petit mal epilepsy, are seen. During a clinical major motor seizure high voltage spikes usually appear in the electroencephalogram starting shortly before the onset of the seizure and persisting until the end of the clonic phase. During the postconvulsive stage large slow waves usually appear and persist for varying periods of time.

B. *Petit Mal Spells.*—We reserve the term petit mal for spells that consist of transient lapses of consciousness lasting usually 5 to 30 seconds associated with bilaterally synchronous three per second spike and wave forms in the electroencephalogram. There may be associated slight clonic movements of the head, eyes, or upper extremities. The patient may stagger or sway a little, but it is extremely rare for him to fall. Occasionally there may be smacking of the lips or urinary incontinence. After the attack is over, the patient is usually alert and able to carry on with previous activity. Petit mal attacks generally recur very frequently, sometimes as often as 100 times daily.

These attacks are encountered almost entirely in young children, particularly females, of high or at least average intelligence, between 4 and 8 years of age. They rarely make their initial appearance after the onset of puberty.

Petit mal spells are the least difficult of all the epileptic seizures for the physician to diagnose. In our experience,[1] the electroencephalogram reveals the classical three per second spike and wave form in essentially 100 per cent of the patients; and a clinical spell can be precipitated in about 90 per cent of the cases with voluntary hyperventilation.

C. *Minor Motor Seizures.*—These attacks generally make their initial appearance early in life, usually between 3 and 12 months of age.

a. *Akinetic type:* When the child is in the sitting position, this type of spell consists of a sudden nod or dropping of the head, usually forward.

In the older child, who is able to stand, it consists of an abrupt loss of all muscle control that results in a precipitous fall. Generally the return of consciousness is immediate and the patient is able to get up almost at once. In some instances, however, he may appear disoriented for a few seconds.

b. *Massive myoclonic type:* This type of seizure varies somewhat in its clinical manifestations, but most frequently consists of a sudden flexion of the head with simultaneous extension of the upper extremities and flexion of the thighs on the abdomen accompanied by a cry. A common variation consists of a sudden generalized tonic spasm with outstretched arms showing slight trembling movements that persist for several seconds or so.

The duration of a minor motor seizure (akinetic or massive myoclonic) is very brief (several seconds). They very often occur in rapid succession and recur frequently during the course of the day. Many children have as many as 50 to 100 such spells or clusters of spells daily. Minor motor seizures occur almost entirely in infants and young children who present evidence of organic brain damage (mental and physical retardation, cerebral palsies, and so forth).

Minor motor seizures are referred to by others as petit mal spells, petit mal variant seizures, lightning majors, abortive grand mal seizures, inhibitory attacks, static attacks, and salaam spells. Lennox[2] includes them in his petit mal triad. Gibbs, Fleming, and Gibbs[3] classify minor motor spells as infantile spasms.

The electroencephalographic abnormalities which are most commonly observed in patients with minor motor seizures have been referred to as "hypsarhythmia" by Gibbs, Fleming, and Gibbs.[3] During an interseizure record, these abnormalities consist of very high voltage, random slow waves and spikes. The electroencephalographic pattern that accompanies a clinical attack usually consists of a discharge of fast waves and high voltage spikes.

D. *Psychomotor Seizures.*—A psychomotor seizure is a bizarre and variable type of epileptic seizure characterized by abnormal and inappropriate behavior associated with some clouding of consciousness and amnesia for the event. Clinically, the seizure usually consists of the sudden performance of some type of abnormal motor or psychic activity or a combination of both.

A very characteristic feature of a psychomotor seizure is the repetitious performance of these bizarre activities. As with all other forms of epilepsy, psychomotor seizures occur in paroxysms. Psychomotor seizures are also referred to in the literature as epileptic equivalents, epileptic variants, epileptic automatisms, epileptic fugues, and temporal lobe epilepsy. A psychomotor seizure should not be confused with the postconvulsive state of confusion or automatism which sometimes occurs immediately following a major motor seizure. Therefore, when a patient is observed in a state of confusion or automatism, he may be having a psychomotor seizure or he may be in a postconvulsive state which has followed an unobserved major motor seizure.

The duration of psychomotor seizures varies considerably. In some instances they persist for a moment or so; at times, they may continue for hours or days. When brief, they are sometimes confused with petit mal spells. Such a differentiation, however, should not be difficult. The return of consciousness following a petit mal spell is almost always abrupt and complete, but following a psychomotor seizure it is generally somewhat prolonged. Paroxysmal runs (usually lasting 5 to 30 seconds) of three per second spike and wave forms are found in the electroencephalograms of essentially all untreated cases of petit mal epilepsy; whereas, in our experience, the electroencephalographic findings in children with psychomotor epilepsy are mostly nonspecific.

When psychomotor seizures occur without other clinical evidence of epilepsy, such as frank convulsions, erroneous diagnoses of hysteria or other behavior disturbances are sometimes made.

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Electroencephalograms in adults with psychomotor epilepsy reveal a very high percentage of abnormal tracings involving the temporal lobe.[4,5] However, temporal lobe abnormalities were present in the electroencephalograms of only 16 (4 per cent) of our 408 children who suffered with clinical psychomotor epileptic seizures. The electroencephalogram was normal in 159 (39 per cent) of these 408 children. In the remaining 233 patients it revealed various types of abnormalities, i.e., abnormally fast and abnormally slow activity, random spiking in areas other than temporal and spike and wave forms other than the classical three per second spike and wave form of petit mal epilepsy. Routine and sleep electroencephalograms were performed on all of these patients.

GENERAL PRINCIPLES OF DRUG THERAPY

1. Treatment should be instituted as soon as the diagnosis has been established. This is the most important aspect of the treatment of epilepsy for the following reasons. First, in most cases, the degree of success in the control of seizures bears a direct relationship to the duration of the epilepsy: the longer the duration the less likely it is that a satisfactory result will be obtained, regardless of the type of therapy instituted. Second, it is important to prevent a recurrence of seizures, particularly those of long duration, because such seizures can produce irreversible brain damage.

2. The selection of the drug of first choice for the treatment of any case of epilepsy depends upon the type of seizure. Two primary considerations are: Some anticonvulsants are more effective in controlling certain types of seizures; on the other hand, some drugs often increase the frequency of certain types of seizures.

For example, phenobarbital and Dilantin are particularly effective in the control of major motor seizures but sometimes accentuate petit mal spells. Tridione, on the other hand, is an effective agent for petit mal spells but sometimes precipitates major seizures or increases the frequency of pre-existing major motor epilepsy.

3. Treatment should begin with one drug, starting with the conventional dosage. The dosage of this drug should be increased, if necessary, until a satisfactory control of seizures is attained or until the limit of tolerance for this drug

has been reached. In some instances it may be necessary to prescribe a second drug, but this should not be done until after it has been determined that the maximal tolerated dosage of the first drug failed to produce a satisfactory clinical response. If the maximal tolerated dosage of the first drug fails to give complete control of seizures but does reduce the frequency or severity to some extent, it should be continued at that same dosage along with the second drug and the dosage of the second drug should be increased, as needed, to tolerance. However, if the maximal tolerated dosage of the first drug fails to help the patient in any manner, it should be gradually withdrawn simultaneously with the administration of the second drug. Occasionally, it may be necessary to prescribe the maximal tolerated dosage of more than two drugs in order to obtain a good control of seizures.

The medication should be taken daily. In most cases it is advisable to prescribe the total daily dosage in equal divided amounts throughout the day. The medication should be given at times of the day, such as with meals and at bedtime, which do not interfere with the patient's routine activities.

4. The therapeutic dosage of anticonvulsant medication varies among patients. The proper dosage for any given patient is that which controls his seizures without producing untoward reactions which interfere with his general well-being. Dosage should not be increased to the point where the patient is so dull that he is more incapacitated by the administration of the drug than by the seizures themselves.

5. The medication should be taken daily, at the same dosage which controlled the seizures, for at least four years after the time of the last seizure. If the four-year period of freedom from seizures should coincide with the onset of puberty, the medication should be continued throughout the adolescent period. This is particularly important in the case of females.

6. The medication should be discontinued very gradually. Following the four-year period of freedom from seizures, dosage should be reduced gradually over a period of one to two years. It is important to note that a sudden withdrawal of anticonvulsant drugs, especially phenobarbital, is a very frequent cause of recurrence of seizures or status epilepticus. Dosage should be increased immediately to the original level if there should be a recurrence of seizures during the period of reduction.

It has been the practice in the past and still is, to some extent today, to advise that all anticonvulsant medication be discontinued for several days or so prior to the performance of an electroencephalogram. We agree that it is probably best to perform electroencephalographic examinations at a time when the patient has received no anticonvulsant medication, since certain drugs occasionally produce changes in the electroencephalogram. However, we do not believe that the information obtained from such electroencephalograms is of sufficient value as to outweigh the likelihood of precipitating status elilepticus or causing a recurrence of seizures by sudden withdrawal of the drug.

7. Periodic physical examinations and at least monthly blood checks should be made on all patients receiving certain drugs which are known to have adversely affected the hemapoietic system, such as Mesantoin, Tridione, and Paradione.

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Complete blood counts should be made on all patients receiving such drugs before the institution of therapy and at least at monthly intervals thereafter. If no abnormalities occur within twelve months, the interval between counts may be extended. It is our policy to discontinue the use of the drug in patients in whom the total white count drops below 3,500, or in whom there is a marked percentage reduction in the neutrophils, or the platelet count drops below 125,000. The drug may be readministered when the blood count returns to normal. In such cases, however, blood counts should be made twice a week for a month or so thereafter. The parents, or the patient, should be instructed to report immediately any sign or symptom of possible damage to the hemapoietic system, such as fever, sore throat, easy bruising, petechiae, ecchymosis, epistaxis, or vaginal bleeding.

Periodic urine examinations should be made on patients receiving drugs which are known to have affected adversely the genitourinary system, such as Tridione and Paradione.

Liver function tests should be performed on patients receiving Phenurone before the institution of therapy and at regular intervals thereafter. The parents, or the patient, should be advised to report immediately to the physician the appearance of jaundice, dark urine, general malaise, fever, gastrointestinal upset or any other disturbance which may be indicative of a beginning hepatitis. Phenurone should be employed with caution in any individual with a history of previous liver damage.

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TREATMENT OF SPECIFIC TYPES OF EPILEPTIC SEIZURES

The following discussion (including Tables I, II, and III) deals with those anticonvulsant drugs which were found to be of significant value in the treatment of our patients. Only those drugs which were available for general usage at the time of this writing are included in this section. Some drugs which have been reported to be effective by other authors, and some which are still in the experimental stage are discussed in a subsequent section of this paper.

TABLE I. DRUGS FOR CONTROL OF MAJOR MOTOR SEIZURES

(*Listed in order of preference**)
Phenobarbital (or Mebaral†)
Dilantin
Mysoline
Bromide
Gemonil
Mesantoin

*Preference is based on relative effectiveness, toxicity, and cost of the drug.
†Mebaral is given to those patients who manifest untoward reactions with phenobarbital.

A. *Major Motor (Grand Mal) Seizures.*—The anticonvulsant drugs which were of significant value in the treatment of major motor epilepsy in our patients are shown in Table I. Let us suppose that we have to prescribe for a 7-year-old

child with major seizures. Such a patient should be given phenobarbital. The initial starting dosage of phenobarbital for a patient of this age is 32 mg. three times a day. The dosage should be increased according to the clinical response of the seizures and the patient's tolerance to the drug. The appearance of marked drowsiness generally indicates that the maximal tolerated dosage has been surpassed. If the maximal tolerated dosage of phenobarbital reduces the frequency or severity of the seizures to some extent but does not produce a completely satisfactory clinical response, it should be continued and Dilantin should be added to the therapeutic regimen. If, however, the maximal dosage of phenobarbital does not favorably affect the patient's condition, it should be gradually withdrawn. The usual initial starting dosage of Dilantin for a patient of this age is 100 mg. two times a day. The dosage of Dilantin should be increased according to the clinical response and the patient's tolerance. Diplopia and/or ataxia are the usual initial symptoms of overdosage of Dilantin. If a satisfactory response is not attained with the maximal dosages of phenobarbital plus Dilantin, other drugs (listed in Table I) should be prescribed. It should be remembered that each drug ought to be given an adequate trial with maximal tolerated dosage before it is dismissed as an unsatisfactory therapeutic agent.

B. *Petit Mal Spells.*—Table II shows the anticonvulsant drugs which were of significant value in the treatment of petit mal epilepsy in our patients.

TABLE II. DRUGS FOR THE CONTROL OF PETIT MAL SPELLS

(3 PER SECOND SPIKE AND WAVE DYSRHYTHMIA)
(*Listed in order of preference**)
Benzedrine (or Dexedrine) sulfate
Paradione
Tridione
Dimedione†

*Preference is based on relative effectiveness, toxicity, and cost of the drug.

†At the time of this writing, Dimedione could be purchased only from Leo Pharmaceutical Products, Lovens Kemiske Fabrik, Bronskojvej 19, Copenhagen, Denmark. This drug is placed at the bottom of the list because of the difficulty in obtaining it in this country.

In our experience, Tridione is the most effective anticonvulsant for the control of petit mal spells. The major disadvantage of Tridione, and to a lesser extent of Paradione, is the toxic effect on the hematopoietic system. The difficulty in obtaining Dimedione makes it of limited use in this country. For these reasons we prefer to start treatment of patients with petit mal with either Benzedrine or Dexedrine sulfate. These drugs are much less effective than either Tridione or Paradione but, since they are essentially innocuous, we believe that it is advisable to give one of them a trial before Paradione or Tridione is prescribed.

It is important that all patients with petit mal epilepsy be given the conventional dosage of drugs such as phenobarbital, Mebaral, Dilantin, or Mysoline in addition to the drug which is prescribed for the control of the petit mal spells. The reason for this combined therapy is that patients who suffer with petit mal

epilepsy are prone to develop major seizures. It has been our experience that such a plan of treatment prevents the occurrence of major seizures in many instances.[7]

We prescribe phenobarbital alone for the first month to determine the patient's tolerance to this drug, and also whether there is an increase in frequency of the petit mal spells. (Both phenobarbital and Dilantin increase the frequency of petit mal spells in some patients.) Mebaral, Dilantin, or Mysoline should be given to those patients who react adversely to phenobarbital. The patient's tolerance to these latter drugs should also be determined in the same manner as for the phenobarbital. The anti-petit mal drug (Table II) should be added to the therapeutic regimen when the tolerated "prophylactic" major motor anticonvulsant (phenobarbital, Mebaral, Dilantin or Mysoline) has been selected.

The dosage of the anti-petit mal drug should be increased according to the effect on seizures and the patient's tolerance to the drug. Other drugs, listed in Table II, should be administered, if necessary, in the same manner as described for the treatment of major motor epilepsy. The same dosage of the so-called "prophylactic" major motor anticonvulsant should be given throughout the entire period of treatment. However, if the patient subsequently should develop major seizures, the dosage of this drug should be increased.

C. *Minor Motor Seizures.*—Minor motor attacks are the most difficult epileptic seizures to control with anticonvulsant drugs. We have had an occasional good result with phenobarbital (or Mebaral), bromides, Benzedrine (or Dexedrine) sulfate, Miltown, or Milontin.

Treatment should begin with one of these drugs and other drugs should be prescribed, if necessary, in the same manner as described for the treatment of major motor seizures. In our experience, a ketogenic diet is the best therapy for minor motor epilepsy.[1]

D. *Psychomotor Seizures.*—Psychomotor seizures frequently are very resistant to anticonvulsant therapy. Table III shows the list of drugs which are helpful in some cases. Phenurone is the most effective drug currently available for the control of psychomotor seizures, but since this drug has been shown to be toxic, Dilantin is our drug of first choice for the treatment of such seizures.

TABLE III. DRUGS FOR THE CONTROL OF PSYCHOMOTOR SEIZURES

(*Listed in order of preference**)
Dilantin
Phenobarbital (or Mebaral†)
Benzedrine (or Dexedrine) sulfate
Mysoline
Mesantoin
Tridione
Phenurone

*Preference is based on relative effectiveness, toxicity, and cost of the drug.
†Mebaral is given to those patients who manifest untoward reactions with phenobarbital.

Therefore, we recommend that treatment of each patient with psychomotor epilepsy begins with Dilantin and that the dosage be increased, if necessary, to tolerance. If the maximum tolerated dosage of Dilantin fails to satisfactorily control the patient's seizures, other drugs (Table III) should be administered in the same manner as described for the treatment of major motor seizures. Phenurone should be prescribed only after all other anticonvulsants have failed.

ANTICONVULSANT DRUGS

A. *Bromides.*—Within recent years the use of bromide as a treatment for epilepsy has diminished, probably because of the enthusiasm for, and the effectiveness of, some of the newer drugs. However, in our clinic, bromide is still considered to be a valuable anticonvulsant. Based on the treatment of approximately 700 patients, our findings indicate that it is an exceedingly effective drug for the control of major motor seizures, particularly those associated with organic brain damage. Bromide is also of some value in the treatment of minor motor seizures, but is essentially ineffective in other types of epilepsy.

The technique for the administration of bromide is not as simple as that of phenobarbital. It has been shown that an increase in the intake of sodium chloride diminishes the accumulation of bromide, the bromide ion being replaced by chloride.[8-11] Therefore, the effectiveness of bromide therapy necessitates a lowered, but fairly constant intake of table salt (NaCl). When bromides are used, the parents of epileptic children should be instructed to withhold salt in the cooking of foods and not to serve foods of high salt content. When there is unusual salt loss, as from vomiting or excessive perspiration, the bromide intake should be reduced or temporarily discontinued. At such times it is advisable to substitute one of the other anticonvulsants such as phenobarbital until the bromides are readministered.

1. *Dosage:* In contrast to phenobarbital the full effect of bromides may not be seen for at least one to two weeks after the institution of therapy. For this reason it may be desirable, in those patients who have frequent seizures, to use phenobarbital during the preliminary period of treatment and to discontinue it gradually after the bromide dosage has become stabilized.

The therapeutic dosage of bromide varies for different children and can be ascertained only by trial. Any of the bromide salts may be used. However, we have found that a solution containing an equal amount of sodium, potassium and ammonium bromide is exceedingly effective (Three Bromide Elixir N.F. Each cubic centimeter contains 80 mg. of each of these three bromides).

The average daily dosages employed in the treatment of our patients are: starting dosage of 320 mg. two times daily and maximum dosage of 640 mg. three times daily for children under 6 years of age, and starting dosage of 320 mg. three times daily and maximum dosage of 1,000 mg. three times daily for children over 6 years.

The plan of treatment should begin with the starting dosage of bromide. The dosage should be increased, if necessary, at weekly intervals and at the same time a blood bromide level should be obtained. It has been our experience

that generally a satisfactory therapeutic blood bromide level ranges between 19 to 24 meq. per liter (150 to 190 mg. per cent). However, in some of our patients the seizures were controlled with bromide levels as low as 10 meq. per liter (80 mg. per cent); again, in others it was necessary that the level be as high as 35 meq. per liter (280 mg. per cent) before a good clinical response was obtained. This is in agreement with the experience of others[9,12-14] in the treatment of adult epileptics.

2. *Bromide excretion:* Bromide excretion takes place slowly, and primarily by the way of the kidneys. We made serial blood bromide determinations on a group of our patients and found relatively high levels for as long as ten to fourteen days after the drug had been discontinued. The slow excretion of bromide from the body probably explains why status epilepticus rarely occurs if a few doses of bromides are missed or if it is discontinued abruptly. This is in distinct contrast to phenobarbital therapy which, if abruptly withdrawn, is frequently followed by a recurrence of seizures or status epilepticus. Since bromide is almost entirely excreted by the kidneys, the presence of either renal damage or reduced urinary flow contraindicates its administration.

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3. *Untoward reactions:* It has been our experience that infants and children tolerate bromides exceedingly well, and, with carefully supervised administration, toxicity is negligible. Drowsiness and acneiform rashes were the only two significant side reactions observed in our patients. Psychoses and neurologic manifestations, reported in adults receiving bromides, were not observed in any of our patients.

Drowsiness is an indication of overdosage. This rarely occurs until the blood bromide level exceeds 19 meq. per liter (150 mg. per cent). It is likely to occur during hot weather when perspiration is marked. Fluctuations in the intake of salt in the food may also bring about an accumulation of bromides and consequently cause drowsiness.

A reduction in the dosage of bromide or the administration of additional sodium chloride and a generous intake of fluid will usually bring about improvement of mild drowsiness within the course of five to ten days. However, in the case of extremely marked drowsiness or coma, bromides should be discontinued immediately. Specific therapy consists in the administration of sodium chloride to hasten bromide elimination. Sodium chloride is given by mouth, as a rule, but if this is impossible, it may be given by hypodermoclysis or intravenous infusion of a sterile 0.9 per cent solution. The dose varies with the severity of the poisoning and the response of the patient, but from 40 to 80 ml. of saline solution per kilogram of body weight should be given daily in divided amounts in addition to the sodium chloride ordinarily contained in the diet.

Although bromides rarely cause skin rashes in pre-adolescent children, they produce an acneiform rash in about 25 per cent of adolescent children. Preexisting acne is generally made much worse by bromides. The actual level of bromide in the blood bears no relationship to the development of acne. This cutaneous eruption probably represents a specific sensitivity to the drug.

The margin of safety in bromide therapy, in our experience, appears to be considerable. This is an important consideration, as many physicians are not

in a position to make blood bromide determinations. Acute bromide poisoning rarely occurs, since an amount sufficient to raise the blood bromide to a toxic level could hardly be ingested without vomiting.[11] Death from bromism, without complicating factors such as chronic renal or heart disease, must be exceedingly rare. Goodman and Gilman[15] state that: "Bromide concentrations in the serum as high as 50 meq. per liter (400 mg. per cent) have occurred, but these unusually high levels are not long compatible with life." However, a partial review of the literature revealed a number of reports in which bromide levels of 50 to 59 meq. per liter (400 to 470 mg. per cent) were found in adults, with recovery.[16-18] We have observed two children in whom levels of 51 meq. per liter (408 mg. per cent) and 49 meq. per liter (390 mg. per cent), respectively, were found. With adequate therapy both of these patients had uneventful recoveries. It has been our experience that the long continued use of bromides even at high levels does not cause any permanent damage to the brain or other organs.

B. *Phenobarbital.*—Phenobarbital (Luminal) is still the most commonly used drug for the treatment of epilepsy. It has definite advantages in that it is the least toxic of all the anticonvulsants, its action starts within an hour or so after ingestion, it is inexpensive and can be used without the necessity of periodic physical and laboratory examinations so essential for the safe use of certain of the newer drugs.

Phenobarbital is exceedingly effective in the control of major motor seizures. It is also of some value for the treatment of minor motor and psychomotor epilepsy. However, it is essentially ineffective in controlling petit mal spells and occasionally accentuates the frequency of these spells.

1. *Dosage:* The average daily dosages of phenobarbital used in the treatment of our patients are: starting dosage of 16 mg. three times daily and maximum dosage of 32 mg. three times daily for children under 3 years of age; starting dosage of 32 mg. two times daily and maximum dosage of 65 mg. three times daily for children between 3 and 6 years; and starting dosage of 32 mg. three times daily and maximum dosage of 100 mg. three times daily for children over 6 years of age.

The effectiveness of a single dose of phenobarbital extends over a relatively short time (6 to 12 hours) so that three or four widely spaced dosages a day are desirable. Absolute regularity in administration of this drug is essential, for the effects of omitting even two or three doses a day may cause a recurrence of seizures or status epilepticus.

2. *Untoward reactions:* In our group of patients the only two significant side reactions were drowsiness or excitation.

Drowsiness is not a toxic reaction, but merely a symptom of overdosage. It can usually be alleviated by a reduction of dosage. It is advisable to administer small daily dosages of amphetamine sulfate to those patients whose seizures are controlled only with amounts of phenobarbital which cause drowsiness before the dosage of the phenobarbital is reduced.

Although phenobarbital is generally considered to be a sedative drug, it is important to note that it causes excitation in some patients. Increased

irritability and restlessness appeared simultaneously with the administration of this drug in approximately 15 per cent of our patients. It was necessary to discontinue the use of phenobarbital in about 10 per cent of these patients because of this excitation reaction. The stimulating effect of phenobarbital is not related to dosage. It appears to be due to a specific sensitivity to the drug.

Judging from our experiences, phenobarbital only rarely causes skin rashes in children. At least 8,000 of our patients have received this drug sometime during the course of their illness and in only five instances did we encounter a skin rash (maculopapular in type) which was thought to be caused by the phenobarbital. Exfoliative dermatitis has been reported by Welton.[19] Severe and fatal phenobarbital eruptions have been reported by Sneddon and Leishman.[20]

Based on our own experience and on review of the literature, we feel that there is no definite indication that phenobarbital adversely affects the hemapoietic or genitourinary system. Constipation occurs frequently with this drug as with other sedative drugs.

It should be re-emphasized that a sudden withdrawal of phenobarbital is a frequent cause of a recurrence of seizures or status epilepticus. Fox[21] reports that a sudden cessation of phenobarbital therapy leads to an increase in the number of seizures in over 70 per cent of patients. This reaction can be largely overcome by a very gradual decrease in the dosage of phenobarbital.

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C. *Mebaral.*—Mebaral (Mephobarbital) chemically is N-methylethylphenylbarbituric acid. This drug was first introduced in Europe in 1929 under the name of Prominal.

Our experience with Mebaral indicates that it is not as effective an anticonvulsant as phenobarbital. In our clinic we limit the use of Mebaral to those patients who manifest untoward reactions in association with phenobarbital therapy.

1. *Available preparations—dosage:* Mebaral is dispensed in tablets containing 32 mg., 50 mg., 100 mg., and 200 mg. of the drug.

The average daily dosages of Mebaral used in the treatment of our patients are: starting dosage of 32 mg. three times daily and maximum dose of 64 mg. three times daily for children under 3 years of age; starting dosage of 64 mg. two times daily and maximum dosage of 130 mg. three times daily for children between 3 and 6 years; and starting dosage of 64 mg. three times daily and maximum dosage of 200 mg. three times daily for children over 6 years.

D. *Gemonil.*—Gemonil (Metharbital) chemically is 5, 5-diethyl-l-methylbarbituric acid. Perlstein[22] was the first to report on the use of this drug in the treatment of epilepsy. He observed good results in patients with "seizures due to organic brain diseases." Peterman[23] reported favorable results in major motor epilepsy.

Our experience with this drug, based on the treatment of 208 patients who suffered with all types of epileptic seizures, indicates that it is of some value in the control of major motor seizures, but that it is by no means as effective as phenobarbital or Mebaral.

Judging from our experiences and those of others,[22,23] it appears that this drug is relatively free of side effects. Except for drowsiness and morbilliform rashes in a few cases, no significant untoward reactions have been observed.

1. *Available preparations—dosage:* Gemonil is dispensed in a 100 mg. tablet.

The average daily dosages of Gemonil used in the treatment of our patients are: starting dosage of 50 mg. three times daily and maximum dosage of 100 mg. three times daily for children under 6 years of age; and starting dosage of 100 mg. three times daily and maximum dosage of 200 mg. three times daily for children over 6 years.

E. *Dilantin.*—The official preparation is diphenylhydantoin sodium (phenytoin sodium), U.S.P., (Dilantin sodium) N.N.R. In Brazil, this drug is known as Epelin; in Great Britain, Uruguay, and British Territories as Epanutin, and in the other Latin American countries as Epamin.

Dilantin is an excellent drug for controlling major motor (grand mal) epileptic seizures. However, in selecting an anticonvulsant we base our choice on a comparison with other drugs in terms of effectiveness, toxicity, and cost. Therefore, in our clinic, phenobarbital is the drug of first choice for the control of major seizures. We prescribe Dilantin for those patients whose seizures are not controlled satisfactorily with maximum dosages of phenobarbital.

Phenurone is the most effective anticonvulsant now available for the control of psychomotor seizures but, since this drug has proved toxic, Dilantin is our drug of first choice for the treatment of psychomotor epilepsy.

In our experience Dilantin is of little, if any, value in controlling minor motor seizures or petit mal spells (three per second spike and wave dysrhythmia). It sometimes increases the frequency of petit mal attacks.

Walker and Kirkpatrick[24] described good results with Dilantin in the treatment of a group of children with behavior problems associated with abnormalities in the electroencephalograms. On the other hand, Pasamanick[25] did not observe any improvement in a group of children with similar disturbances treated in the same way.

Putnam and Rothenberg[26] reported seizure control in a group of epileptic patients in whom intensive effects were produced by administration of massive doses (up to 4 Gm. daily) of Dilantin. Ketosis from starvation was allowed to develop and the patients were given inhalations of a carbon dioxide-oxygen mixture every hour. The period of sleep usually lasted 4 days and the entire treatment about 2 weeks. We have had no experience with this form of therapy.

Favorable results with the parenteral use of Dilantin in preventing seizures in neurosurgical operations and in the treatment of status epilepticus were reported by Murphy and Schwab.[27] These workers recommend that, in severe status epilepticus, an intravenous dose of Dilantin of 150 to 250 mg. be given, and if the seizures do not stop, a subsequent dose of 100 to 150 mg. be injected a half hour later. The injection should be given at a rate not exceeding 4 c.c. or 100 mg. per minute.

Dilantin is of limited value for the treatment of convulsive disorders of infants and young children, since it is frequently impossible to determine the

maximal tolerated dosage in children of this age. For example, one may have considerable difficulty in deciding whether Dilantin is responsible for unsteadiness of gait in a 14-month-old child just beginning to walk and it would be almost impossible to determine whether such a child was suffering from diplopia.

1. *Available preparations—dosage:* Dilantin is dispensed in 32 mg. and 100 mg. capsules. (The 32 mg. capsule is pink-banded and the 100 mg. is orange-banded.) A special orange opaque-banded 100 mg. capsule known as Dilantin D.A. (delayed absorption) also is available. This preparation is of value in the treatment of epileptic seizures which occur in the early morning hours. In such cases, Dilantin D.A. should be prescribed at bedtime. Dilantin is prepared also in a cream-colored triangular tablet (50 mg.) and in a soluble gelatin capsule containing a suspension of 100 mg. of Dilantin in vegetable oil. This latter preparation should be given to those patients who develop gastrointestinal disturbances with other forms of Dilantin. A liquid suspension of Dilantin, each 4 c.c. of which contains 100 mg., is available for oral use. Diphenylhydantoin is supplied in powdered form in a sterile vial (Dilantin Sodium S.V.) which contains 250 mg. of the drug for parenteral use. An ampule containing 5 c.c. of special solvent is supplied with the package.

The average daily dosages used in the treatment of our patients are: starting dosage of 32 mg. three times daily and maximum dosage of 100 mg. three times daily for children under 6 years of age; and starting dosage of 100 mg. two times daily and maximum dosage of 200 mg. three times daily for children over 6 years.

2. *Untoward reactions:* Disturbances of equilibrium (ataxia or unsteadiness of gait) and diplopia are the most frequent untoward reactions encountered during Dilantin therapy. These disorders, due to overdosage, almost always disappear within one to two weeks after the dosage of Dilantin has been reduced. However, we have observed 3 patients with ataxia persisting for approximately six months after the drug had been withdrawn completely. Many of our patients became ataxic and complained of diplopia for several days, for no apparent reason, after having tolerated daily maintenance doses of Dilantin for prolonged periods of time. It seems probable that there was a temporary increased accumulation of Dilantin during these intervals. Therefore, one need not necessarily reduce the established maintenance dose unless signs of overdosage persist for longer than three or four days.

Nystagmus, dysarthria, and drowsiness may be encountered in patients overtreated with Dilantin. They usually disappear soon after the dose of the drug is reduced to the tolerated level. Drowsiness is not seen as commonly with Dilantin as with the barbiturates.

Tremors have been observed in a few of our patients. Some also complain of dizziness or a "sensation of walking on air." Several patients have had headaches which appeared to be related to the Dilantin. Four of our children exhibited behavior disturbances which disappeared soon after the drug was discontinued. Toxic amblyopia has also been reported.[28]

Skin rashes are encountered frequently, a measles-like eruption being the most common. This cutaneous reaction usually appears ten to fourteen days

after the initial ingestion of Dilantin and is frequently associated with elevation of temperature and occasionally with lymphadenopathy. This exanthem sometimes involves the mouth and throat. At times one may have some difficulty differentiating such a Dilantin rash from that of rubeola.

Other types of skin lesions are also occasionally seen in association with Dilantin therapy. A few of our patients have had scarlatiniform or urticarial rashes. Two developed purpuric (non-thrombocytopenic) rashes and two suffered from a severe exfoliative dermatitis. One developed thrombocytopenic purpura when she was taking Paradione and Dilantin,[29] but it appeared that Paradione was the etiologic agent. Van Wyk and Hoffman[30] reported a fatal case of exfoliative dermatitis. Heller and Sloane[31] described a case of erythema bullosum malignans in a child 9 years of age, Ellis[32] a case of ectodermosis erosiva pluriorificialis, and Ritchie and Kolb[33] a fatal case of hemorrhagic erythema multiforme. Mandelbaum and Kane reported[34] the case of a patient who suffered from pyrexia, exfoliative dermatitis, and considerable enlargement of the liver and spleen. Two cases of hepatitis with jaundice, pyrexia, and exfoliative dermatitis have been observed[35,36] with one death.[36]

There can be no doubt that measles-like rashes are caused by Dilantin. Approximately 5 per cent of our patients developed such rashes ten to fourteen days after the institution of Dilantin therapy. However, I believe that no definite conclusions concerning the etiology of some of the other reported skin lesions are justified. Nevertheless, the physician should be cognizant of the possibility of more severe cutaneous reactions to Dilantin than is generally appreciated.

The measles-like rashes are not related to the dosage and probably indicate a sensitivity to the drug, since patients develop such reactions as frequently with small as with large dosages of Dilantin.

The drug should be discontinued immediately at the appearance of any type of cutaneous reaction. The same dosage may be represcribed to those patients with the milder type of rashes (measles-like and the scarlatiniform type), but only after the rash has completely disappeared. About 25 per cent of our patients have had a recurrence of the rash with the second administration of Dilantin. There was no relationship between the dosage of the drug prescribed the second time and occurrence of the rash. It is inadvisable to continue use of the drug in those patients in whom purpuric rashes, exfoliative dermatitis, and other serious skin reactions appear.

Hyperplasia of the gums from Dilantin was first reported by Kimball.[37] This disturbance has occurred in approximately 15 per cent of our patients. Hyperplastic gums are usually quite firm and faintly pink in color. Some of our patients complain of bleeding occurring either spontaneously or in association with brushing of the teeth. In a few instances the hyperplastic tissue was so extensive that it covered the cutting edges of the teeth. Two of our adult epileptic patients with marked gingival hyperplasia had, on their own accord, all their teeth extracted. Although they continued to take Dilantin for many years thereafter the hyperplasia receded spontaneously and has not recurred. This finding suggests the possibility that Dilantin hyperplasia of the gums does not occur in the absence of teeth.

The histologic changes in Dilantin gingival hyperplasia have been reported.[38,39] At present, no other tissue in the body is known to react in a similar manner.

The occurrence or degree of hyperplasia of the gums is not related to the dosage of Dilantin. This reaction probably represents specific sensitivity to the drug. In most cases, the gums return to normal within a year or so after the drug has been completely withdrawn.

Gingival hyperplasia can be reduced somewhat by strict oral hygiene and daily vigorous massage. Repeated excision of excessive hyperplastic tissue is helpful in some instances. The occurrence of hyperplasia of the gums itself is not an indication for the discontinuance of Dilantin. In some instances, however, it may be necessary to withdraw the drug because the hyperplastic tissue does not respond to corrective measures and becomes so marked that it interferes with chewing or is disfiguring.

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Hypertrichosis has occurred in association with Dilantin therapy in 16 of our epileptic children. The term "hirsutism" has been used by Wilkins[40] to denote excessive growth of sexual hair of a masculine pattern, while "hypertrichosis" has been applied to the more general growth of excessive body hair.

These 16 patients (14 girls and 2 boys) varied in age from 3 to 14 years. The hypertrichosis appeared two to three months after the beginning of Dilantin therapy. It occurred predominantly on the extensor surfaces of the extremities but in several patients it appeared also on the trunk and face. The distribution of the hair did not simulate a sex pattern in any case. Three patients, in whom the hypertrichosis had raised a suspicion of an endocrine disturbance, were studied by Wilkins, who found no evidence of hormonal disturbance or elevation of the urinary 17-ketosteroids.

In 12 of these 16 patients the hypertrichosis disappeared within one year after withdrawal of the Dilantin but it has persisted in the remaining 4 who have been maintained on the drug. The growth of the hair was related neither to the dosage of Dilantin nor to the type of epilepsy.

Gastrointestinal disturbances such as a "heavy feeling in the stomach," nausea or vomiting are also encountered in some patients but they are usually relatively minor. In many instances, they can be prevented by prescribing Dilantin either with or after meals or by the use of a gelatin capsule suspension of Dilantin in vegetable oil. However, in an occasional case these symptoms are so severe that it is impossible for the patient to retain the drug or any food.

Obstinate constipation is seen very frequently in patients who have been receiving Dilantin for prolonged periods of time. Anorexia and abdominal pain are occasionally observed. Two patients who suffered with hepatitis, jaundice, pyrexia, and exfoliative dermatitis have been reported,[35,36] one of them died.[36]

None of our patients has complained of any symptoms referable to the genitourinary system and no abnormalities were found in the urine in approximately 500 patients examined. Finkelman and Arieff,[41] however, reported six instances of albuminuria in 44 patients receiving Dilantin. Hematoporphyrin has also been reported in the urine of 2 patients receiving the drug.[42]

Complete blood counts were made on approximately 500 of our patients over a two-year period during which time they were receiving Dilantin. No significant disturbances were noted in any of these patients. In a few instances there was a transient reduction in the total number of white blood cells, but the differential counts in these cases did not show any decrease in the relative percentage of polymorphonuclear leukocytes. Eosinophilia was observed in a few cases. One of our patients presented a marked diminution of platelets when she was taking both Paradione and Dilantin.[29] It is probable that Paradione was the etiologic agent. Otherwise, there was no evidence of diminution of platelets in any case. Agranulocytosis has been observed in a few patients.[43-45] Megaloblastic anemia has also been reported.[46-51]

Hematologic reactions to Dilantin have heretofore been considered as exceedingly rare. However, in view of these recently reported cases of megaloblastic anemia, the physician should be alert to this disturbance.

No clinical evidence of cardiac disturbances was observed in any of our patients. Evidence of myocardial damage and changes in the electrocardiogram have been reported.[41,52,53] A change in the cardiac rate was observed in 3 patients who showed toxic signs while taking Dilantin.[54] Bradycardia was reported in 2 patients, one after five weeks, the other after three months of medication with Dilantin.[42] Two fatal cases of periarteritis nodosa have been reported.[30,55] One of these patients[55] was also taking Mesantoin at the same time.

F. *Mesantoin.*—Mesantoin (5-ethyl-3 methyl-5-phenylhydantoin) is closely related chemically and pharmacologically to Dilantin (diphenylhydantoin). Loscalzo[56] in 1945 was the first to report the effectiveness of this drug in controlling major motor epileptic seizures. Subsequently, other investigators reported similar findings.[57-62]

Our experience with Mesantoin, based on the treatment of 642 patients, also indicates that it is an effective anticonvulsant for the control of major motor seizures. It is also of some value for the treatment of psychomotor epilepsy. None of our patients with petit mal or minor motor spells were significantly benefited by this drug.

1. *Available preparations—dosage:* Mesantoin is available as a scored pink tablet which contains 100 mg. of the drug.

The average daily dosages of Mesantoin used in the treatment of our patients are: starting dosage of 50 mg. three times daily and maximum dosage of 200 mg. three times daily for children under 6 years of age; and starting dosage of 100 mg. three times daily and maximum dosage of 400 mg. three times daily for children over 6 years.

2. *Untoward reactions:* Drowsiness was the most common side reaction observed in our group of patients. The appearance of drowsiness indicates that the maximum tolerable dosage of the drug has been exceeded. This effect can usually be alleviated by reduction in dosage. Ataxia, diplopia, and nystagmus were seen only in an occasional patient. Two of our patients exhibited mental confusion and another a psychotic disturbance during the course of Mesantoin therapy.

Mesantoin causes measles-like skin rashes similar to those seen with Dilantin. About 5 per cent of our patients suffered from such cutaneous reactions. Purpuric rashes associated with abnormally low platelet counts were seen in 4 patients. Another developed an exfoliative dermatitis during the course of Mesantoin therapy. Fatal dermatitides have been reported in several patients.[63,64] Hunter and Jenkins[65] observed patchy pigmentation in association with Mesantoin therapy. Hyperplasia of the gums, which is seen so frequently with Dilantin, was not observed in any of our patients.

The most significant and alarming toxic effect of Mesantoin is hematologic. Approximately 7 per cent of our patients showed a significant reduction in the leukocyte count and a percentage reduction of polymorphonuclear cells during the course of Mesantoin therapy. Two patients developed a pancytopenia. We experienced no hematologic fatalities in our patients, but deaths from pancytopenia have been reported.[66-73] Best and Paul[74] concluded that hypoplasia of the bone marrow may develop in two weeks to thirteen months, with an average interval of five months after the beginning of therapy.

Kozol[63] reported a death due to acute hepatitis. A fatal case of periarteritis nodosa has also been reported.[55] However, this patient was also taking Dilantin at the same time. No significant gastrointestinal, genitourinary, or cardiovascular disturbances were encountered in any of our patients.

G. *Mysoline.*—Mysoline (Primidone) chemically is 5-phenyl-5-ethyl-hexahydropyrimidine-4:6 dione. The first report dealing with the use of Mysoline in the treatment of epilepsy was presented in 1952 by Handley and Stewart.[75] Many other investigators[76-101] subsequently used this drug for the control of epileptic seizures.

Our results[101] with this drug, based on the treatment of 486 patients, indicate that it is primarily of value in the treatment of major motor epilepsy. Many other investigators have had similar experiences. None of our patients with petit mal, minor motor, or psychomotor seizures were helped significantly by this drug. However, other workers[76,79,81,89,100] have reported good results in petit mal and psychomotor epilepsy.

1. *Untoward reactions:* The most common side reaction was drowsiness, which occurred in 160 of our 486 patients. It varied in degree from mild, transient sleepiness to severe lethargy. In the majority of cases the drowsiness appeared within the first few days of the beginning of Mysoline therapy. In many cases it came on after the first few doses were taken. Several patients stated that they slept for approximately twenty-four hours after taking single tablets. In 127 patients the drowsiness disappeared spontaneously within several weeks of its onset, and treatment with the same dosage of the drug was not interrupted. In 33 patients the dosage necessary to control the convulsions produced such severe lethargy that the drug had to be discontinued. Timberlake and coworkers[98] suggested that the drowsiness might be minimized if treatment was started with one half a tablet (125 mg.) at bedtime and the dose very gradually increased thereafter as indicated.

Dizziness was reported in 22 of our patients and ataxia was noted in 19. It was necessary to discontinue the therapy in 9 patients who complained of dizziness and in 4 who presented ataxia. In the remainder of the patients, the dizziness and ataxia cleared up spontaneously within one or two weeks, and treatment with the same dosage was not interrupted.

Generalized morbilliform skin rashes occurred in 2 patients six and ten days, respectively, after the first dose. In both, the rash disappeared within ten days of withdrawal of the drug. The same dosage was given again to both patients, and the rash did not reappear.

Diplopia occurred in 2 patients, personality changes in 2, and nausea and vomiting in 4. These disturbances were transient and of little consequence.

In addition to the untoward reactions observed by us, a wide variety of disturbances have been reported: edema of the eyelids,[93] painful gums,[93] sexual impotence,[93] slurred speech,[87,93,95] nystagmus,[85,93] paranoid psychosis,[76,81,92] headaches,[95] polyuria,[76] and abdominal pain.[89]

No hematologic disturbances were encountered in any of our patients. However, leukopenia[89,98] and megaloblastic anemia[102] have been reported. To our knowledge no irreversible toxic disturbances have been observed.

2. *Available preparations—dosage:* Mysoline is dispensed in 250 mg. tablets and in a suspension, each teaspoonful of which contains 250 mg. of the drug.

The average daily dosages of Mysoline used in the treatment of our patients are: starting dosage of 62.5 mg. two times daily and maximum dosage of 125 mg. four times daily for children under 3 years of age; starting dosage of 125 mg. two times daily and maximum dosage of 250 mg. four times daily for children between 3 and 6 years; and starting dosage of 250 mg. two times daily and maximum dosage of 500 mg. three times daily for children over 6 years.

H. *Tridione.*—Tridione (Trimethadione) chemically is 3,5,5-trimethyloxazolidine-2,4-dione. The first clinical report dealing with the use of this drug in the treatment of epilepsy was presented by Lennox[103] in 1945. Since that time it has been used extensively by many investigators, who report that it is an excellent anticonvulsant for the control of petit mal and "minor" spells.[104-121] Several workers also describe satisfactory results in the treatment of psychomotor epilepsy.[122-125] Blumberg[126] reported a good result in one patient with abdominal epilepsy. Most physicians agree that Tridione is of little, if any, value for the control of major motor seizures.

Our results, based on the treatment of approximately 1,400 children who suffered with various types of epileptic seizures, revealed that Tridione is primarily of value in the treatment of petit mal epilepsy. The spells of 546 (68 per cent) of our 804 patients who suffered with petit mal epilepsy were completely controlled by the administration of Tridione.[127]

Only rarely were any of our patients with minor motor or psychomotor seizures favorably affected. We prescribed maximum dosages of Tridione to 181 patients with minor motor seizures, and in only an occasional case did we observe a satisfactory result. Gibbs, Fleming, and Gibbs[3] apparently have had similar unfavorable experiences.

Our findings are in general agreement with the opinion of most workers that Tridione is an ineffective drug for the control of major motor epilepsy; indeed, it may predispose some patients to major motor seizures. Fourteen of our patients who suffered with pure petit mal epilepsy had major motor seizures within twenty-four to forty-eight hours of the administration of the drug; Tridione also sometimes increases the frequency of pre-existing major motor seizures.[1,113,128,129]

1. *Untoward reactions:* Photophobia has been the most frequent side reaction observed in our group of patients. Approximately 20 per cent complain of this disturbance during the course of therapy. Diplopia, vertigo, increased irritability and drowsiness are encountered, usually when excessive amounts of the drug are taken. Headaches, insomnia, personality changes, and behavior difficulties have been seen occasionally.

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Skin rashes have occurred in approximately 3 per cent of our patients. Morbilliform and urticarial rashes are the most frequent types observed. In one patient a hemorrhagic cutaneous reaction developed in association with pancytopenia. Eczematoid and acneiform rashes were occasionally seen. Cutaneous reactions, consisting of an erythema multiforme of pluriorificial type and exfoliative dermatitis, have been reported.[130-132] Two of our patients had generalized swelling of the joints associated with pain and slightly elevated temperature beginning soon after the administration of Tridione; investigations for rheumatic fever were negative. In both cases the swollen joints and fever disappeared on withdrawal of Tridione and recurred when the drug was readministered. Forsey and Black[133] reported angioneurotic edema in one patient in association with Tridione therapy.

Hiccoughs occurred in about 4 per cent of our patients. This disturbance usually makes its appearance a week or two after the initial administration of the drug. It usually persists for two or three days and generally disappears spontaneously. Nausea, vomiting and abdominal pain are encountered occasionally. Leard, Greer, and Kaufman[132] reported a case of hepatitis associated with exfoliative dermatitis and abnormal bone-marrow activity occurring during Tridione therapy.

The most serious toxic effect of Tridione is disturbance of bone-marrow activity: leukopenia, neutropenia, agranulocytosis, thrombocytopenia, pancytopenia, and hypoplastic anemia have been observed. Bleeding gums, epistaxis, petechial hemorrhages, vaginal bleeding or retinal hemorrhages are occasionally the initial presenting symptoms of blood dyscrasias occurring with Tridione. Abnormal hematopoiesis usually becomes manifest at some time during the first year on the drug and most frequently during the first six months. We have had no deaths from hematologic disorders, but fatal cases have been reported by others.[134-142]

None of our patients complained of any symptoms referable to the genitourinary system. Studies of the urine in a large number showed no abnormalities during the course of Tridione therapy. Nephrosis[143-147] has been reported, with one death.[147] Millichap and Kirman[148] reported microscopic hematuria and cellular casts in 8 of 12 patients treated with Tridione.

No toxic signs or symptoms referable to the cardiovascular system have been observed in any of our patients. To our knowledge, none has been reported by others.

2. *Available preparations—dosage:* Tridione is dispensed in 300 mg. capsules, in 150 mg. Dulcet tablets and in a solution, each teaspoonful of which contains 150 mg. of the drug.

The average daily dosages of Tridione used in treatment of our patients are: starting dosage of 150 mg. two times daily and maximum dosage of 300 mg. three times daily for children under 6 years of age; and starting dosage of 300 mg. two times daily and maximum dosage of 600 mg. three times daily for children over 6 years.

I. *Paradione.*—Paradione (Paramethadione) chemically is 3-5-dimethyl-5-ethyloxazolidine-2-4-dione. The first report dealing with the use of this drug in the treatment of epilepsy was presented by Davis and Lennox[149] in 1947. Since that time this drug has been used fairly extensively but not as much as Tridione.[1,113,129,133,150-152]

The reported results indicate that Paradione is effective in the treatment of petit mal epilepsy but less so than Tridione. Several physicians reported equivocal results in the treatment of psychomotor epilepsy.

Our findings, based on the treatment of approximately 600 children with all types of seizures, showed that this drug was effective only in the control of petit mal epilepsy. Ninety-eight (31 per cent) of 216 of our patients with petit mal epilepsy were completely relieved of their spells by the administration of Paradione[127]; none of those with psychomotor, major motor or minor motor seizures were affected favorably. Gibbs, Fleming, and Gibbs[3] have had similar results with minor motor spells.

The untoward reactions of Paradione are in general similar to those of Tridione but are less frequent and usually less severe. Hematologic disturbances similar to those caused by Tridione have been observed but none of these cases, to our knowledge, has been fatal.[1,113,129,149-152] Nephrosis has also been reported[1,150,153] with one death.[1]

1. *Available preparations—dosage:* Paradione is dispensed in gelatin capsules of two strengths: 150 mg. and 300 mg. It is also supplied in a 50 c.c. solution (65 per cent alcohol), each cubic centimeter of which contains 300 mg. of the drug.

The average daily dosages of Paradione used in the treatment of our patients are: starting dosage of 150 mg. two times daily and maximum dosage of 300 mg. three times daily for children under 6 years of age; and starting dosage of 300 mg. two times daily and maximum dosage of 600 mg. three times daily for children over 6 years.

J. *Benzedrine Sulfate.*—Our results with Benzedrine sulfate (racemic amphetamine sulfate), based on the treatment of 684 patients who suffered with various types of epileptic seizures, indicate that it is of some value for the treatment of petit mal epilepsy. However, it is by no means as effective as the dione

drugs (Tridione and Paradione). We found that Benzedrine sulfate gave complete control of petit mal spells in 38 (11 per cent) of 344 of our patients with this form of epilepsy.[6] This drug also has been shown to be helpful in minor motor and psychomotor epilepsy and has been used to counteract the drowsiness produced by sedative drugs.[154-157]

1. *Untoward reactions:* The untoward reactions observed in our group of patients who were treated with Benzedrine sulfate were of little consequence. Insomnia occurred in 7 patients. This disturbance can usually be corrected by prescribing the last dose of the drug not later than 4 P.M. It was necessary to discontinue the use of the drug in 4 patients because of marked loss of weight. Increased irritability and restlessness occurred in 6 patients and tremors in another. These reactions can almost always be alleviated by a reduction in the dosage. Transient glycosuria was observed in 4 patients.

2. *Available preparations—dosage:* Benzedrine sulfate is dispensed in tablets containing 5 mg. and 10 mg. of the drug. It is also supplied in a capsule (Benzedrine sulfate Spansule) which contains 15 mg. of the drug distributed among hundreds of tiny pellets with varying disintegration times. The drug is released gradually, yet continuously, over a period of eight to ten hours.

The average daily dosages of Benzedrine sulfate used in the treatment of our patients are: starting dosage of 2.5 mg. two times daily and maximum dosage of 5 mg. three times daily for children under 6 years of age; and starting dosage of 5 mg. two times daily and maximum dosage of 15 mg. three times daily for children over 6 years.

K. *Dexedrine Sulfate.*—Dexedrine sulfate (dextro-amphetamine sulfate) is the dextrorotatory isomer of Benzedrine sulfate. The indications for the use of this drug and also the side reactions are the same as those for Benzedrine sulfate.

1. *Available preparations—dosage:* Dexedrine sulfate is dispensed in a 5 mg. tablet and in an elixir, each 5 c.c. of which contains 5 mg. of the drug. It is also prepared in capsules (Dexedrine sulfate Spansule) which contain 10 mg. and 15 mg. of the drug.

The average daily dosages of Dexedrine sulfate used in the treatment of our patients are: starting dosage of 2.5 mg. daily and maximum dosage of 2.5 mg. three times daily for children under 6 years of age; and starting dosage of 2.5 mg. two times daily and maximum dosage of 7.5 mg. three times daily for children over 6 years.

L. *Milontin.*—Favorable results with Milontin (N-methyl-5-phenyl-succinimide) in the treatment of petit mal epilepsy were first reported by Zimmerman[158] and subsequently by others.[159-167] Chao and Fields[168] described good results in some cases of petit mal epilepsy with the combined use of Milontin and Tridione. On the other hand, Smith and Forster,[169] Peterman,[170] and Doyle and co-workers[171] were unable to demonstrate any permanent control of petit mal epilepsy (three per second spike and wave dysrhythmia) with this drug.

Milontin was prescribed to 310 of our patients who suffered with various types of epileptic seizures. Our findings indicate that this drug is essentially ineffective in completely controlling petit mal, major motor and psychomotor epilepsy, but that it is of some value in minor motor epilepsy.

The significant side reactions which have been observed in association with Milontin therapy are: drowsiness, ataxia or unsteadiness of gait, irritability, restlessness, rash, nausea, vomiting, anorexia, headache, urinary frequency or burning, and microscopical hematuria.

1. *Available preparations—dosage:* This drug is dispensed in a 500 mg. capsule and in a suspension, each 4 c.c. of which contains 250 mg. of the drug.

The average daily dosages of Milontin used in the treatment of our patients are: starting dosage of 250 mg. two times daily and maximum dosage of 500 mg. three times daily for children under 6 years of age, and starting dosage of 500 mg. two times daily and maximum dosage of 1,000 mg. four times daily for children over 6 years.

M. *Diamox.*—The first report, to our knowledge, dealing with the use of Diamox (acetazolamide) in the treatment of epilepsy was presented by Bergstrom and co-workers[172] in 1952. These investigators reported 50 to 100 per cent seizure control in 8 of 42 patients who failed to respond to other anticonvulsant drugs. In 1954, Merlis[173] reported some good results in a group of 47 adults with epilepsy treated with Diamox. In 1956, Lombroso and Davidson[174] reported the following results obtained on 126 epileptic patients who received Diamox from three months to three years: in 37 per cent the seizures were reduced at least 90 per cent; in 17 per cent they were reduced 50 to 90 per cent, and in 46 per cent they were reduced 50 per cent or less. These authors stated that benefit was greatest in those patients having three per second spike and wave discharges in the electroencephalogram.

Diamox was administered for two to six months to 58 of our patients who suffered with very frequent seizures of various types.[175] There was a temporary decrease (for several weeks or so) in the frequency of seizures in a few patients. However, this drug did not control completely the spells of any of the 58 patients treated.

No significant side reactions were observed in any of our patients. However, agranulocytosis,[176] thrombocytopenia,[177] and renal lesions of sulfonamide type[178] have been reported.

1. *Available preparations—dosage:* Diamox is dispensed in a 250 mg. tablet.

The average daily dosages of Diamox used in the treatment of our patients are: starting dosage of 125 mg. three times daily and maximum dosage of 250 mg. three times daily for children under 6 years of age; and starting dosage of 250 mg. two times daily and maximum dosage of 250 mg. five times daily for children over 6 years.

N. *Phenurone.*—Phenurone (Phenacemide) chemically is phenylacetylurea. The first clinical report dealing with the use of this drug in the treatment of epilepsy was presented in 1949 by Gibbs and associates,[179] who found it particularly

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effective in patients with psychomotor epilepsy. Subsequently, a large number of publications have called attention to the value of Phenurone in the treatment of epilepsy (particularly psychomotor epilepsy) and also to the considerable hazard involved in its use.[180-202]

Our results, based on the treatment of 411 patients, indicate that Phenurone is primarily of value in the treatment of psychomotor epilepsy. None of our patients with major motor, minor motor or petit mal spells were helped significantly by this drug.

1. *Untoward reactions:* The most common side reaction encountered was an adverse change in personality or behavior, which occurred in 61 (15 per cent) of our 411 patients. Destructiveness, belligerence, marked irritability, restlessness and depression were the changes most commonly observed. Suicidal tendencies, paranoia, acute psychotic states and delusions of persecution have also been reported.[194] It was necessary to discontinue the drug in 54 (11 per cent) of our patients because of marked changes in personality or behavior. In one patient, an 8-year-old boy, the changes were so marked that institutionalization was seriously considered. He became belligerent and destructive, slept very little, remained out late at night and paid no attention to his parents or schoolteachers. His symptoms, however, diminished promptly after the drug was withdrawn and disappeared completely in about four weeks.

Psychic changes occur most commonly within the first four to six weeks after the initial administration of Phenurone. Judging from our experience there is no relationship between the dosage of the drug and the occurrence of changes of personality or behavior.

Twenty (5 per cent) of our patients complained of headaches or a "feeling of fullness in the head." The headache was generally quite severe and appeared most commonly within the first few days after the institution of therapy. It was necessary to discontinue Phenurone in 8 (2 per cent) of our patients because of this disturbance. Drowsiness, insomnia, dizziness and parasthesias were seen occasionally. Insenstivity to pain was reported in one patient.[190]

Skin rashes of maculopapular or scarlatiniform type occurred in 12 (3 per cent) of our patients. These cutaneous eruptions appeared most commonly ten to fourteen days after the initial ingestion of the drug and were occasionally accompanied by an elevation of temperature. These skin rashes were not related to the dosage and probably indicate sensitivity, since they appear as frequently with small as with larger dosages. The skin rash disappeared in each instance about four to seven days after the drug had been completely withdrawn. Acneiform lesions also have been reported by others.[188]

Hepatitis occurred during the course of Phenurone therapy in 5 of our patients. Tyler and King[194] reported the occurrence of hepatitis in 2 per cent of a group of 1,562 patients treated with this drug. To our knowledge, there have been six reported hepatic deaths occurring during the course of Phenurone therapy.[183,188,196,199,201] In one of these cases there was also marked involvement of the kidneys.[183] Although these 6 patients were receiving other anticonvulsants at the same time or had been treated previously with other antiepileptic drugs, it seems definite that the Phenurone was the cause of death in each case.

Disturbances such as anorexia, loss of weight, vomiting, and vague abdominal pains were encountered in 32 (8 per cent) of our patients. It was necessary to discontinue the drug in 10 patients because of anorexia and loss of weight.

Fourteen of our patients developed a transient proteinuria within the first two weeks or so after receiving Phenurone. No blood cells or casts were present in any of these instances. None of these patients showed any signs or symptoms of urinary disorders before the drug was prescribed. Two were hospitalized for a detailed study of kidney function, including pyelography. No impairment of kidney function was demonstrated in either. The nature of the protein was not determined.

Acetonuria and glycosuria have been observed in patients receiving Phenurone.[194] Nephritis[194] and a fatal case of hepatorenal syndrome[183] also have been reported.

Routine blood counts were made monthly on all of our 411 patients during the entire period in which they received Phenurone. One hundred and ninety-eight of these patients have been receiving the drug continuously for four or five years. No abnormalities were encountered in any case. However, blood changes such as leukopenia, leukocytosis, low platelet count, and granulocytopenia have been reported by others.[194] Two fatal cases of aplastic anemia also have been reported.[181,184] The role of Phenurone in producing aplastic anemia in those 2 cases is not definite. Both of them had been treated previously with Mesantoin, a drug which is known to affect adversely the hemapoietic system. It is possible that the aplastic anemia was caused by the Mesantoin. It is true that the Mesantoin had been discontinued some weeks before the onset of toxic symptoms. However, we have seen hemapoietic disturbances in several patients weeks after Mesantoin had been discontinued completely.

2. *Available preparations—dosage:* Phenurone is dispensed in 500 mg. grooved tablets and in 300 mg. enteric coated tablets.

The average daily dosages of Phenurone used in the treatment of our patients are: starting dosage of 250 mg. three times daily and maximum dosage of 1,000 mg. three times daily for children under 6 years of age; and starting dosage of 500 mg. three times daily and maximum dosage of 2,000 mg. three times daily for children over 6 years.

O. *Miscellaneous Drugs.*—In 1942, McQuarrie, Anderson, and Ziegler[203] reported beneficial effects in 2 patients with epilepsy who had been treated with *desoxycorticosterone acetate.* Since that time, other investigators have demonstrated the anticonvulsant effects of this hormone in animals.[204,205] In 1951, Gordan and Aird[206] reported a definite diminution in the frequency of seizures in 10 patients when 4 to 15 mg. of desoxycorticosterone acetate per day was administered sublingually. Klein and Livingston[207] observed temporary improvement in a small group of epileptic children who were treated with *ACTH* and *cortisone.*

Hawkes[208] and Kaplan and Moslanka[209] reported good results with *Hibicon* (N-benzyl-B-chloropropionamide) in the treatment of a small group of patients with major motor epilepsy. Our findings[210] indicate that this drug is of very

little, if any, value in the treatment of major motor epilepsy. Hibicon was administered to 49 of our patients who suffered with major motor epileptic seizures. The spells were not controlled in any. Peterman[170] also found Hibicon to be essentially ineffective in the treatment of epilepsy. Hibicon was withdrawn from the market by the manufacturer.

Glutamine, an ammonium salt of glutamic acid, is reported to have produced seizure control in several patients. Tower[211] described not only clinical but electroencephalographic improvement.

Stamps, Gibbs, and Haase[212] reported "dramatic" seizure control and electroencephalographic improvement in 25 patients treated with *Aureomycin*. On the other hand, Peterman[170] treated 18 patients with Aureomycin and observed no favorable results. Aureomycin failed to give control in 11 children whom we treated.

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Perlstein[213] found *Prenderol* effective in controlling petit mal epilepsy. He reported that this drug was even more effective when retarding agents such as cream or other fats or oils were given simultaneously with each dose of Prenderol because of the short-lived activity of this drug. However, this drug failed to provide satisfactory control of seizures for 19 of our patients with petit mal epilepsy.

Ellebjerg,[214] Lund,[215] and Ellebjerg, Lund, and Saxe[216] reported complete seizure control in 31 per cent of 123 patients treated with *Dimedione*. No irreversible toxic reactions were observed in any of these patients. Fifty-one of our patients with petit mal epilepsy were treated with this drug and the spells were controlled in 10 (20 per cent).[127] No significant untoward reactions were observed.

Themisone (atrolactamide) was not available for general use at the time of this writing. It has been reported to be effective in grand mal and psychomotor epilepsy.[217] We have had no experience with this drug.

Pyridoxine (vitamin B_6) controlled the convulsions which occurred in infants fed milk preparations deficient in vitamin B_6[1,218,219] and in adults and animals given isoniazid experimentally.[220] Pyridoxine also was effective in eliminating seizures in the patient reported by Hunt and co-workers,[221] presumed to have increased vitamin B_6 requirement on a congenital basis. However, our findings, and also those of Fox and Tullidge,[223] indicate that this vitamin is of no value in the control of epileptic seizures. On the other hand, Ernsting and Ferwerda[224] reported favorable results in 8 of 14 epileptic patients treated with Pyridoxine.

In 1950, Livingston and Sweet[225] reported good seizure control with the use of *Nuvarone* (3-methyl-5-phenylhydantoin) in the treatment of 88 patients. Subsequently, this drug proved to be toxic to the hemapoietic system[226,227] and was withdrawn from use. *Thiantoin sodium* (sodium 5-phenyl-5-thienylhydantoinate) also had proved to be an effective anticonvulsant. However, this drug was withdrawn from use after 4 fatal cases of hepatic necrosis were reported to have occurred during its administration.[228,229]

We have not had good results with the use of *ammonium chloride* in the treatment of epilepsy. Peterman[170] also reports poor results with this drug.

However, Kant and co-workers[230] observed favorable results with ammonium chloride as adjunctive therapy in the treatment of a group of epileptic patients.

Meprobamate (Miltown, Equanil) was administered to 121 of our patients who suffered with epileptic seizures of various types. This drug was helpful in some of those with minor motor epilepsy, but was essentially ineffective in controlling other types of seizures. However, Perlstein[231] reported good results in petit mal epilepsy.

This drug is dispensed in a 400 mg. tablet. The dosage administered to our patients varied from 400 mg. daily to 2,400 mg. daily. No significant untoward reactions were observed. A complete report of our results with the use of meprobamate in the treatment of epilepsy is now in press.

Celontin (PM-396) chemically is N-methyl-a, a-methylphenylsuccinimide. This drug was not available for general use at the time of this writing. Zimmerman and Burgemeister[232-234] reported good results with Celontin in the control of petit mal epilepsy. Our results[235] with this drug, based on the treatment of 136 patients who suffered with epileptic seizures of various types, showed that it was somewhat effective in controlling minor motor and psychomotor epilepsy. However, patients with petit mal or major motor seizures were not significantly benefited. No significant side reactions were observed.

Peganone (AC-695) chemically is ethylphenylhydantoin. This drug was not available for general usage at the time of this writing. Our results,[236] based on the treatment of 108 patients, indicate that it has definite effectiveness in major motor epilepsy and to a lesser extent in psychomotor epilepsy. None of the patients with petit mal or minor motor seizures was benefited significantly. It appears that Peganone is relatively free of side effects. Except for a skin rash in one patient, no significant untoward reactions were encountered. However, by comparative tests, we found that Peganone is by no means as effective an anticonvulsant as Dilantin.

We agree with Peterman[170] who states that the use of *glutamic acid* (in epilepsy) has not survived the passage of time. We[1] prescribed glutamic acid to approximately 200 children who suffered with all types of epileptic seizures and in only an occasional case did we observe a favorable anticonvulsant effect. Some of these patients were treated with glutamic acid alone; others received glutamic acid in addition to other anticonvulsants, including phenobarbital and Dilantin. We also made serial intelligence tests on a group of 14 mentally retarded epileptic children who were being treated with large doses of glutamic acid. Each of these patients was followed for at least two years. No significant rise in the intelligence quotient was observed in any case.

Chlorpromazine (Thorazine) was administered to 125 of our patients who suffered with various types of epileptic seizures. The spells were not controlled in any. However, this drug was of considerable value in alleviating the behavior disturbances which are so commonly seen in epileptic children.[237-239] Some patients were given chlorpromazine alone; others received this drug in addition to maximum dosages of anticonvulsant drugs, such as phenobarbital or Dilantin. The dosage of chlorpromazine administered varied from 20 mg. daily to 300 mg. daily. We have had almost identical experiences with the

use of *reserpine* (Serpasil). A detailed report dealing with the use of the various tranquilizing drugs in the treatment of epilepsy is now in press.

Atabrine (quinacrine) is reported as being of value in the control of petit mal attacks by several workers.[240,241] This drug failed to control the petit mal attacks in 12 patients whom we treated.

The following preparations which contain two or more drugs are available: (a) *Mebroin* is dispensed in a tablet which contains 90 mg. of Mebaral and 60 mg. of diphenylhydantoin; (b) *Hydantal* is dispensed in a tablet which contains 100 mg. of Mesantoin and 20 mg. of phenobarbital; (c) *Phelantin Kapseals* is dispensed in a capsule which contains 30 mg. of phenobarbital, 2.5 mg. of desoxyephedrine hydrochloride and 100 mg. of diphenylhydantoin; (d) *Dilantin-Phenobarbital Kapseals* is dispensed in a capsule which contains 16 mg. of phenobarbital and 100 mg. of diphenylhydantoin.

In our own clinic we rarely prescribe a preparation which contains a fixed dosage of drugs. The disadvantage of such preparations is that they do not permit satisfactory regulation of dosage of each constituent. Many patients may require a higher or lower dose of one of the drugs which are included in a combined preparation. Another disadvantage is that the physician may have considerable difficulty in determining which of the compounds is responsible for an untoward reaction, such as a rash.

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SUMMARY

1. The classification of epileptic seizures used at The Johns Hopkins Hospital Epilepsy Clinic is presented.

2. The general principles of drug therapy for childhood epilepsy are discussed.

3. The methods and anticonvulsant drugs employed for the treatment of specific types of epileptic seizures are given.

4. The various anticonvulsant drugs are discussed in detail: available preparations, dosage, indications for use, and untoward reactions.

REFERENCES

1. Livingston, S.: The Diagnosis and Treatment of Convulsive Disorders in Children, Springfield, Ill., 1954, Charles C Thomas, Publishers.
2. Lennox, W. G.: Petit Mal Epilepsies: Their Treatment With Tridione, J.A.M.A. **129:**1069, 1945.
3. Gibbs, E. L., Fleming, M. M., and Gibbs, F. A.: Diagnosis and Prognosis of Hypsarhythmia and Infantile Spasms, Pediatrics **13:**66, 1954.
4. Gibbs, E. L., Gibbs, F. A., and Fustor, B.: Psychomotor Epilepsy, Arch. Neurol. & Psychiat. **60:**331, 1948.
5. Bailey, P., and Gibbs, F. A.: The Surgical Treatment of Psychomotor Epilepsy, J.A.M.A. **145:**365, 1951.
6. Livingston, S., and Boks, L. L.: Use of the Dione Drugs (Propazone, Tridione, Paradione, Dimedione and Malidone) in the Treatment of Epilepsy of Children, New England J. Med. **253:**138, 1955.
7. Livingston, S.: Results of Combined Therapy for Petit Mal Epilepsy, In Press.
8. Ulrich, A.: The Bromide-chloride Treatment of Epilepsy, Med. J. & Rec. **126:** pp. 41, 88, 156, and 245, 1927.
9. Notkin, J.: Chloride-bromide Treatment in Epilepsy, Arch. Neurol. & Psychiat. **21:**165, 1929.
10. Wallace, G. B., and Brodie, B. B.: The Distribution of Administered Bromide in Comparison With Chloride and Its Relation to Body Fluids, J. Pharmacol. & Exper. Therap. **65:**214, 1939.

11. Palmer, J. W., and Clarke, H. T.: The Elimination of Bromides From the Blood Stream, J. Biol. Chem. **99**:435, 1932-33.
12. Diethelm, O.: On Bromide Intoxication, J. Nerv. & Ment. Dis. **71**:151 and 278, 1930.
13. Pollock, L. J.: Remissions of Attacks in Epilepsy Treated With Sodium Bromide, J.A.M.A. **110**:632, 1938.
14. Weir, E. G.: The Influence of the Serum Bromide Concentration Upon the Distribution of Bromide Ion Between Serum and Spinal Fluid, Am. J. Physiol. **137**:109, 1942.
15. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, 1955, The Macmillan Company.
16. Detweiler, H. K.: Bromide Intoxication, Canad. M.A.J. **48**:309, 1943.
17. Campbell, J. D.: Bromide Intoxication: Report of 36 Cases, South. M.J. **42**:967, 1949.
18. Sensenbach, W.: Bromide Intoxication, J.A.M.A. **125**:769, 1944.
19. Welton, D. G.: Exfoliative Dermatitis and Hepatitis Due to Phenobarbital, J.A.M.A. **143**:232, 1950.
20. Sneddon, I. B., and Leishman, A. W. D.: Severe and Fatal Phenobarbitone Eruptions, Brit. M. J. **1**:1276, 1952.
21. Fox, J. T.: Luminal Sodium in the Treatment of Epilepsy, Lancet **2**:589, 1927.
22. Perlstein, M. A.: Gemonil (5-5-diethyl 1-methyl barbituric acid). New Drug for Convulsive and Related Disorders, Pediatrics **5**:448, 1950.
23. Peterman, M. A.: Treatment of Convulsions in Childhood, Am. J. Dis. Child. **84**:409, 1952.
24. Walker, C. F., and Kirkpatrick, B. B.: Dilantin (Diphenylhydantoin) Treatment for Behavior Problem Children With Abnormal Electroencephalograms, Am. J. Psychiat. **103**:484, 1947.
25. Pasamanick, B.: Anticonvulsant Drug Therapy of Behavior Problem Children With Abnormal Electroencephalograms, Arch. Neurol. & Psychiat. **65**:752, 1951.
26. Putnam, T. J., and Rothenberg, S. F.: Results of Intensive (Narcosis) and Standard Medical Treatment of Epilepsy, J.A.M.A. **152**:1400, 1953.
27. Murphy, J. T., and Schwab, R. S.: Diphenylhydantoin (Dilantin) Sodium Used Parenterally in Control of Convulsions, J.A.M.A. **160**:385, 1956.
28. Levitt, J. M., and Blonstein, M.: Toxic Amblyopia Resulting From Sodium Diphenyl Hydantoinate, New York State J. Med. **40**:1538, 1940.
29. Reichelderfer, T. E., Pearson, P. H., and Livingston, S.: Thrombocytopenic Purpura Occurring in Association With Paradione (Paramethadione) and Dilantin Sodium (Phenytoin Sodium) Therapy, J. Pediat. **43**:42, 1952.
30. Van Wyk, J. J., and Hoffman, C. R.: Periarteritis Nodosa: A Case of Fatal Exfoliative Dermatitis Resulting From "Dilatin Sodium" Sensitization, Arch. Int. Med. **81**:605, 1948.
31. Heller, C., and Sloane, M.: Erythema Bullosum Malignans Following Dilantin Therapy, Pediatrics **5**:836, 1950.
32. Ellis, F. A.: Reactions to Nirvanol, Phenytoin Sodium and Phenobarbital. Report of a Case of Ectodermosis Erosiva Pluriorificialis Following the Ingestion of Phenytoin Sodium, South. M. J. **36**:575, 1943.
33. Ritchie, E. B., and Kolb, W.: Reaction to Sodium Diphenyl Hydantoinate (Dilantin Sodium), Arch. Dermat. & Syph. **46**:856, 1942.
34. Mandelbaum, H., and Kane, L. J.: Dilantin Sodium Poisoning, Arch. Neurol. & Psychiat. **45**:769, 1941.
35. Chaiken, B. H., Goldberg, R. I., and Segal, J. P.: Dilantin Sensitivity. Report of a Case of Hepatitis With Jaundice, Pyrexia and Exfoliative Dermatitis, New England J. Med. **242**:897, 1950.
36. Gropper, A. L.: Diphenylhydantoin Sensitivity. Report of Fatal Case With Hepatitis and Exfoliative Dermatitis, New England J. Med. **254**:522, 1956.
37. Kimball, O. P.: The Treatment of Epilepsy With Sodium Diphenyl Hydantoinate, J.A.M.A. **112**:1244, 1939.
38. Esterberg, H. L., and White, P. H.: Sodium Dilantin Gingival Hyperplasia, J.A.D.A. **32**:16, 1945.
39. Crome, L.: The Histological Changes in Hydantoinate Gingivitis, J. Clin. Path. **5**:244, 1954.
40. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., 1950, Charles C Thomas, Publisher.
41. Finkelman, I., and Arieff, A. J.: Untoward Effects of Phenytoin Sodium in Epilepsy, J.A.M.A. **118**:1209, 1942.
42. Williamson, B. A. M.: Severe Toxic Effects of Sodium Diphenyl Hydantoinate in Mentally Defective Epileptics, J. Ment. Sc. **86**:981, 1940.
43. Aring, C. D., and Rosenbaum, M.: Ingestion of Large Doses of Dilantin Sodium, Arch. Neurol. & Psychiat. **45**:265, 1941.
44. Dickerson, W. W.: The Present Status of Dilantin Therapy, Am. J. Psychiat. **98**:515, 1942.
45. Schoemperlen, C. B.: Agranulocytosis Due to Dilantin Sodium, Manitoba Med. Rev. **27**:687, 1947.

46. Rhind, E. G., and Varadi, S.: Megaloblastic Anaemia Due to Phenytoin Sodium, Lancet **2**:921, 1953.
47. Webster, J. M.: Megaloblastic Anaemia Due to Phenytoin Sodium, Lancet **2**:1017, 1954.
48. Chalmers, J. M. M., and Boheimer, K.: Megaloblastic Anaemia and Anticonvulsant Therapy, Lancet **2**:920, 1954.
49. Hawkins, C. F., and Meynell, M. J.: Megaloblastic Anaemia Due to Phenytoin Sodium, Lancet **2**:737, 1954.
50. Berlyne, N., and Levene, M.: Megaloblastic Anaemia Following Anticonvulsants, Brit. M. J. **1**:1247, 1955.
51. Ryan, G. M. S., and Forshaw, J. W. B.: Megaloblastic Anaemia Due to Phenytoin Sodium, Brit. M. J. **2**:242, 1955.
52. Loscalzo, A. E.: Treatment of Epileptic Patients With a Combination of 3-Methyl 5-5-Phenylethyl Hydantoin and Phenobarbital, J. Nerv. & Ment. Dis. **101**:537, 1945.
53. Mallach, J. F., Finkelman, I., Arieff, A. J., and Roberts, R. C.: Electrocardiographic Changes Resulting From Dilantin Medication, Northwest. Univ. Bull. Med. School **17**:97, 1943.
54. Williams, D.: Treatment of Epilepsy With Sodium Diphenyl Hydantoinate, Lancet **2**:678, 1939.
55. Frankel, A. L., and Rothermich, N. O.: Polyarteritis Nodosa: A Review Together With Report of a Case Due to Hydantoin Sensitization, Ohio Med. J. **47**:1013, 1951.
56. Loscalzo, A. E.: Treatment of Epileptic Patients With a Combination of 3-Methyl 5-5-Phenylethyl-Hydantoin and Phenobarbital, J. Nerv. & Ment. Dis. **101**:537, 1945.
57. Kozol, H. L.: Epilepsy. Treatment With New Drug: 3-Methyl 5-5-Phenyl-Ethyl-Hydantoin (Phenantoin), Am. J. Psychiat. **103**:154, 1946.
58. Littlejohn, W. S., Little, S. C., and McLallen, C.: The Uses of Methyl-Phenyl-Ethyl-Hydantoin (Mesantoin) in the Treatment of Convulsive Disorders, Dig. Neurol. & Psychiat. **15**:710, 1947.
59. David, N. A., Durkin, L. S., Margason, M. L., and Viele, W. A.: Methyl Hydantoin (Mesantoin) in the Treatment of Epilepsy, J. Nerv. & Ment. Dis. **108**:118, 1948.
60. Fetterman, J. L., and Victoroff, V. M.: Mesantoin in Epilepsy, A Three-Year Study, Dis. Nerv. System **10**:355, 1949.
61. Mallin, A. W., and Gammon, G. D.: A Clinical Evaluation of Mesantoin in Epilepsy, J. Nerv. & Ment. Dis. **118**:193, 1953.
62. Dreyer, R.: Erfahrungen mit Mesantoin, Deutsch. med. Wschr. **79**:1215, 1954.
63. Kozol, H. L.: Mesantoin in Treatment of Epilepsy, Arch. Neurol. & Psychiat. **63**:235, 1950.
64. Ruskin, D. B.: Fulminating Dermatitis Bullosa Medicamentosa Due to "Mesantoin," J.A.M.A. **137**:1031, 1948.
65. Hunter, H., and Jenkins, D.: Occurrence of Skin Pigmentation During Mesantoin Therapy, J.A.M.A. **147**:744, 1951.
66. Aird, R. B.: The Treatment of Epilepsy With Methylphenylethyl Hydantoin (Mesantoin), California Med. **68**:141, 1948.
67. England, N. J., and McEachern, D.: Acute Aplastic Anaemia During Mesantoin Therapy, Canad. M.A.J. **60**:173, 1949.
68. Weller, R. W., and Metcalfe, J.: Fatal Pancytopenia Following the Use of "Mesantoin." Report of a Case, New England J. Med. **241**:17, 1949.
69. Witkind, E., and Waid, M. E.: Aplasia of the Bone Marrow During Mesantoin Therapy, J.A.M.A. **147**:757, 1951.
70. Stillman, S., Bedell, S. G., and Leavitt, D.: Fatal Aplastic Anaemia Associated With Mesantoin: Report of a Case With Autopsy, J. Florida M. A. **37**:496, 1951.
71. Burrell, Z. L.: Fatal Pancytopenia as a Result of Improperly Supervised Mesantoin Therapy, Amer. Pract. & Digest. Treat. **6**:726, 1955.
72. Swartout, R.: Two Cases of Fatal Pancytopenia Following Mesantoin Therapy, California Med. **78**:138, 1953.
73. Benhamou, E., and Albou, A.: Sur deux cas mortels d'anémie aplastique causeé par la Mesantoine (méthyl-phényléthyl-hydantoine), Algerie méd. **56**:389, 1952.
74. Best, W. R.,and Paul, J. T.: Severe Hypoplastic Anemia Following Anticonvulsant Medication: Review of the Literature and Report of a Case, Am. J. Med. **8**:124, 1950.
75. Handley, R.,and Stewart, A. S. R.: Mysoline: New Drug in Treatment of Epilepsy, Lancet **1**:742, 1952.
76. Smith, B. H., and McNaughton, F. L.: Mysoline, New Anticonvulsant Drug: Its Value in Refractory Cases of Epilepsy, Canad. M.A.J. **68**:464, 1953.
77. Butter, A. J. M.: Mysoline in Treatment of Epilepsy, Lancet **1**:1024, 1953.
78. Bogue, J. Y., and Carrington, H. C.: Evaluation of Mysoline: New Anticonvulsant Drug, Brit. J. Pharmacol. **8**:230, 1953.
79. Bonkalo, A., and Arthurs, R. G. S.: Mysoline in Treatment of Epileptic and Non-Epileptic Psychiatric Patients, Canad. M.A.J. **68**:570, 1953.

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6
1957

80. Goodman, L. S., Swinyard, E. A., Brown, W. C., Schiffman, D. O., Grewal, M. A., and Bliss, E. L.: Anticonvulsant Properties of 5-Phenyl-5-Ethyl-Hexahydropyrimidine-4, 6-Dione (Mysoline), A New Antiepileptic, J. Pharmacol. & Exper. Therap. **108**:428, 1953.
81. Whitty, C. W. M.: Value of Primidone in Epilepsy, Brit. M. J. **2**:540, 1953.
82. Doyle, P. J., and Livingston, S.: Use of Mysoline in Treatment of Epilepsy, J. Pediat. **43**:413, 1953.
83. Greenstein, L., and Sapirstein, M. R.: Treatment of Epilepsy With Mysoline, Arch. Neurol. & Psychiat. **70**:469, 1953.
84. Jorgensen, G.: Mysoline, Its Use in Epilepsy, Lancet **2**:835, 1953.
85. Burton-Bradley, B. G.: Report on Mysoline in Treatment of Mental Hospital Epileptics, M. J. Australia **40**:705, 1953.
86. Game, J. A.: Mysoline, Its Use in Epilepsy, M. J. Australia **40**:707, 1953.
87. Selby, G.: Mysoline: Clinical Evaluation of New Drug in Treatment of Refractory Cases of Epilepsy, M. J. Australia **40**:709, 1953.
88. Nathan, P. W.: Primidone in Treatment of Non-Idiopathic Epilepsy, Lancet **1**:21, 1954.
89. Briggs, J. N., and Tucker, J.: Primidone (Mysoline) in Treatment of Clinical Petit Mal in Children, Lancet **1**:19, 1954.
90. Goldin, S.: Toxic Effects of Primidone, Lancet **1**:102, 1954.
91. Swinyard, E. A., Tedeschi, D. H., and Goodman, L. S.: Effect of Liver Damage and Nephrectomy on Anticonvulsant Activity of Mysoline and Phenobarbital, J.A.M.A. **43**:114, 1954.
92. Smith, B., and Forster, F. M.: Mysoline and Milontin: Two New Medicines for Epilepsy, Neurology **4**:137, 1954.
93. Sciarra, D., Carter, S., Vicale, C. T., and Merritt, H. H.: Clinical Evaluation of Primidone (Mysoline), New Anticonvulsant Drug, J.A.M.A. **154**:827, 1954.
94. Pence, L. M.: Mysoline in Epilepsy, Texas State J. Med. **50**:290, 1954.
95. Lyons, J. B., and Liversedge, L. A.: Primidone in Treatment of Epilepsy, Brit. M. J. **2**:625, 1954.
96. Sharpe, D. S.: Primidone in Mental Deficiency Practice, Brit. M. J. **2**:627, 1954.
97. Jorgensen, G.: Epilepsibehandling med mepoline: 187 behandlede tilfaelde, Nord. med. **52**:1400, 1954.
98. Timberlake, W. H., Abbott, J. A., and Schwab, R. S.: Mysoline: Effective Anticonvulsant With Initial Problems of Adjustment, New England J. Med. **252**:304, 1955.
99. Houston, A. B.: Mysoline in Epilepsy, Manitoba Med. Rev. **134**:134, 1955.
100. Brizio, L.: Sul trattamento della epilessia infantile con Mysoline, Clin. pediat. **37**:137, 1955.
101. Livingston, S., and Petersen, D.: Primidone (Mysoline) in the Treatment of Epilepsy, New England J. Med. **254**:327, 1956.
102. Girdwood, R. H., and Lenman, J. A. R.: Megaloblastic Anemia Occurring During Primidone Therapy, Brit. M. J. **1**:146, 1956.
103. Lennox, W. G.: Treatment of Epilepsy, M. Clin. North America **29**:1114, 1945.
104. Thorne, F. C.: Anticonvulsant Action of Tridione, Psychiat. Quart. **19**:686, 1945.
105. Perlstein, M. A., and Andelman, M. B.: Tridione: Its Use in Convulsive and Related Disorders, J. Pediat. **29**:20, 1946.
106. Erickson, T. C., Masten, M. G., and Gilson, W.: Observations on Use of Tridione (3,5,5, Trimethylexazolidine-2,4 Dione) in Treatment of Epilepsy, Tr. Am. Neurol. A. **71**:125, 1946.
107. Merritt, H. H.: Recent Advances in Treatment of Epilepsy, With Particular Emphasis on Use of Tridione, Arch. Neurol. & Psychiat. **57**:130, 1947.
108. Bickel, G.: Le Tridione, Rev. méd. Suisse Rom. **67**:267, 1947.
109. Lennox, W. G.: Tridione in Treatment of Epilepsy, J.A.M.A. **134**:138, 1947.
110. Gibbs, F. A.: New Drugs of Value in Treatment of Epilepsy, Ann. Int. Med. **28**:548, 1947.
111. Nour El Din, G.: Tridione, Translated by Gamal, Roy. Egyptian M.A.J. **30** (Arabic Section):5, 1947.
112. Malin, K. A.: Tridione—New Anti-Epileptic, Svenska läk-tidning. **44**:1700, 1947.
113. Peterman, M. G.: Epilepsy in Childhood: Newer Methods of Diagnosis and Treatment, J.A.M.A. **138**:1012, 1948.
114. Seidman, J.: Médication anticonvulsante: le Tridione, médicamentation du petit mal épileptique, Synthése de séméiologie thérapeutique **1** (R.P.):9, 1948.
115. Butter, A. J. M.: "Tridione" in Treatment of Petit Mal., Brit. M. J. **1**:13, 1948.
116. Ricciardi, R.: II. Tridione, nuovo farmaco antiepilettico, Diagnosi **5**:99, 1949.
117. Verjaal, A.: Tridione in absentol als anti-epilepticum, Nederl. tijdschr. v. geneesk. **92**:1743, 1948.
118. Whitty, C. W. M.: "Tridione" in Treatment of Epilepsy, Brit. M. J. **2**:311, 1949.
119. Bonduelle, M.: Le Tridione: médicament spécifique du petit mal épileptique, Paris méd. Suppl. **2**:51, 1949.
120. Haward, F. C.: Use of "Tridione" in Petit Mal, Brit. M. J. **2**:315, 1949.

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121. Davies, G. R., and Spillane, J. D.: Tridione Therapy in Minor Epilepsy, Brain **72**:140-149, 1949; Am. Practitioner **1**:215, 1950.
122. DeJong, R. N.: Effect of Tridione in Control of Psychomotor Attacks, J.A.M.A. **130**:565, 1946.
123. DeJong, R. N.: Further Observations on the Use of Tridione in the Control of Psychomotor Attacks, Am. J. Psychiat. **103**:162, 1946-47.
124. Forster, F. M.: Therapy in Psychomotor Epilepsy, J.A.M.A. **145**:211, 1951.
125. Merlis, J. K.: Medical Treatment of Psychomotor Epilepsy, Neurology **1**:245, 1951.
126. Blumberg, M. L.: Abdominal Epilepsy: Report of Case Controlled With Tridione, J. Pediat. **45**:89, 1954.
127. Livingston, S., and Boks, L. L.: Use of the Dione Drugs (Propazone, Tridione, Paradione, Dimedione and Malidone) in the Treatment of Epilepsy in Children, New England J. M. **253**:138, 1955.
128. Mustard, H. S., and Livingston, S.: Tridione Therapy in Epilepsy; Review of Results in 156 Patients With Petit Mal Epilepsy With Special Reference to Side Reactions, J. Pediat. **35**:540, 1949.
129. Lennox, M. A.: Drug Treatment of Epilepsy, Connecticut M. J. **12**:1006, 1948.
130. Kerrin, J. C.: Fatalities From Tridione, Lancet **1**:267, 1948.
131. Shaffer, B., and Morris, P.: Severe Erythema Multiforme of Pluriorificial Type (Stevens-Johnson Syndrome) Resulting in Blindness in Patient Treated With Trimethadione (Tridione), Pediatrics **2**:30, 1948.
132. Leard, S. E., Greer, W. E. R., and Kaufman, C. I.: Hepatitis, Exfoliative Dermatitis and Abnormal Bone Marrow Occurring During Tridione Therapy, New England J. Med. **240**:962, 1949.
133. Forsey, R. R., and Black, R. W.: Tridione and Paradione Sensitivity, Canad. M.A.J. **64**:120, 1951.
134. Braithwaite, R. F.: Fatal Case of Agranulocytosis Associated With Tridione Therapy, Brit. M. J. **1**:14, 1948.
135. Best, W. R., and Paul, J. T.: Severe Hypoplastic Anaemia Following Anticonvulsant Medication; Review of Literature and Report of Case, Am. J. Med. **8**:124, 1950.
136. Harrison, F. F., Johnson, R. D., and Ayer, D.: Fatal Aplastic Anemia Following Use of Tridione and Hydantoin, J.A.M.A. **132**:11, 1946.
137. Mackay, R. P., and Gottstein, W. K.: Aplastic Anemia and Agranulocytosis Following Tridione: Fatal Case, J.A.M.A. **132**:13, 1946.
138. Berry, A. N.: Fatality Following "Tridione," South. M. J. **42**:995, 1949.
139. Carnicelli, T. J., and Tedeschi, C. G.: Fatal Acute Pancytopenia Following Tridione Treatment, New England J. Med. **238**:314, 1948.
140. Kaplan, S. R., Levy, G., and Schwartz, S. O.: Fatal Aplastic Anemia Following Tridione Administration, Dis. Nerv. System **10**:339, 1949; Digest Neurol. & Psychiat. **18**:41, 1950.
141. Michelstein, I., and Weiser, N. J.: Fatal Agranulocytosis Due to Trimethadione (Tridione), Arch. Neurol. & Psychiat. **62**:358, 1949.
142. Forster, T. W., Watson, J. W., and Neumark, E.: Agranulocytosis and Thrombocytopenia Following Use of Tridione, Lancet **1**:517, 1949.
143. Barnett, H. L., Simons, D. J., and Wells, R. E.: Nephrotic Syndrome Occurring During Tridione Therapy, Am. J. Med. **4**:760, 1948.
144. White, J. C.: Nephrosis Occurring During Trimethadione Therapy, J.A.M.A. **139**:376 1949.
145. Nabarro, J. D. N., and Rosenheim, M. L.: Nephrotic Syndrome Complicating Tridione (Troxidone) Therapy, Lancet **1**:1091, 1952.
146. Tegelaers, W. H. H., and Tiddens, H.: Nephrosis Due to Tridione (Trimethadione oxazolidinedione Derivative) Therapy of Epilepsy: Case, Maandschr. v. kindergeneesk. **20**:23, 1952.
147. Briggs, J. N., and Emery, J. L.: Toxic Effects of Tridione, Lancet **1**:59, 1949.
148. Millichap, J. G., and Kirman, B. H.: Nephrotoxic Effects of Drugs Used in Treatment of Petit Mal, Lancet **1**:1074, 1953.
149. Davis, J. P., and Lennox, W. G.: Effect of Trimethyloxazolidine-Dione and Dimethyloxazolidine-Dione on Seizures and on Blood, A. Research Nerv. & Ment. Dis., Proc. **26**:423, 1947.
150. Davis, J. P., and Lennox, W. G.: Comparison of Paradione and Tridione in Treatment of Epilepsy, J. Pediat. **34**:273, 1949.
151. A.M.A. Council on Pharmacy and Chemistry. Paramethadione (Paradione), J.A.M.A. **143**:970, 1950.
152. Foster, F. M., and Borkowski, W. J.: Paridione in Treatment of Petit Mal Epilepsy, Am. Practitioner **1**:406, 1950.
153. Wren, J. C., and Nutt, R. L.: Nephrotic Syndrome Occurring During Paramethadione Therapy: Report of Case With Clinical Remission, J.A.M.A. **153**:918, 1953.
154. Cohen, B., and Myerson, A.: The Effective Use of Phenobarbital and Benzedrine Sulfate (Amphetamine Sulfate) in the Treatment of Epilepsy, Am. J. Psychiat. **95**:371, 1938-39.

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6
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155. Cook, G. H., and Dole, J. A.: A Report on the Use of Phenobarbital and Benzedrine Sulfate in the Treatment of Epilepsy, Dis. Nerv. System **3**:366, 1942.
156. Robinson, L. J.: Amphetamine (Benzedrine) Sulfate as a Corrective for the Depression of Sedative Medication in Epilepsy, Am. J. Psychiat. **98**:215, 1941-42.
157. Stone, T. T., Finkelman, I., and Arieff, A. J.: A Note on the Usefulness of Analeptic Drugs Combined in the Treatment of Epilepsy, Am. J. Psychiat. **96**:1377, 1939-40.
158. Zimmerman, F. T.: Use of Methylphenylsuccinimide in Treatment of Petit Mal Epilepsy, A.M.A. Arch. Neurol. & Psychiat. **66**:156, 1951.
159. Millichap, J. G.: Milontin—A New Drug in the Treatment of Petit Mal, Lancet **2**:907, 1952.
160. Lereboullet, J., Pluvinage, R., Vidart, L., and Thomas, J.: Le traitement du petit mal par le methylphenyl succinimide. Bullet. mém. Soc. méd. hôp. Paris **69**:87, 1953.
161. Chen, G. C., and Ensor, C. R.: The Combined Anticonvulsant Activity and Toxicity of Dilantin and N-Methyl-5-Phenylsuccinimide (Laboratory Study), J. Lab. & Clin. Med. **41**:78, 1953.
162. Forrer, G. R.: Use of Milontin in Treatment of Mental Patients With Petit Mal Convulsive Disorders, J. Mich. State Med. Soc. **53**:275, 1954.
163. Lemere, F.: Milontin in Treatment of Petit Mal Epilepsy, Northwest Medicine **53**:482, 1954.
164. Carter, C. H.: Use of Milontin in the Control of Petit Mal Epilepsy, Neurology **4**:935, 1954.
165. Davidson, D. T., Lombroso, C., and Markham, C. H.: Methylphenylsuccinimide (Milontin) in Epilepsy, New England J. M. **253**:173, 1955.
166. Zimmerman, F. T., and Burgemeister, B. B.: Drugs Used in Treatment of Patients With Petit Mal Epilepsy. A Serial Evaluation of New and Standard Drugs With Alternate Placebo Base Lines in Identical Cases, J.A.M.A. **157**:1194, 1955.
167. Zimmerman, F. T.: Milontin in the Treatment of Epilepsy, N. Y. State J. Med. **55**:2338, 1955.
168. Chao, D., and Fields, W. S.: Combined Drug Therapy in Petit Mal Epilepsy, J. Pediat. **45**:293, 1954.
169. Smith, B., and Forster, F. M.: Mysoline and Milontin—Two New Medicines for Epilepsy, Neurology **4**:137, 1954.
170. Peterman, M. G.: Present Status of Idiopathic Epilepsy, J. Pediat. **44**:624, 1954.
171. Doyle, P. J., Livingston, S., and Pearson, P. H.: Use of Milontin in the Treatment of Petit Mal Epilepsy (Three per Second Spike and Wave Dysrhythmia), J. Pediat. **43**:164, 1953.
172. Bergstrom, W. H., Carzoli, R. F., Lombroso, C., Davidson, D. T., and Wallace, W. M.: Observations on the Metabolic and Clinical Effects of Carbonic-Anhydrase Inhibitors in Epileptics, Am. J. Dis. Child. **84**:771, 1952.
173. Merlis, S.: Diamox: A Carbonic Anhydrase Inhibitor; Its Use in Epilepsy, Neurology **4**:863, 1954.
174. Lombroso, C. T., and Davidson, D. T.: Further Evaluation of Acetazolamide (Diamox) in the Treatment of Epilepsy, J.A.M.A. **160**:268, 1956.
175. Livingston, S., Petersen, D. C., and Boks, L. L.: Ineffectiveness of Diamox in the Treatment of Childhood Epilepsy, Pediatrics **17**:541, 1956.
176. Pearson, J. R., Binder, C. I., and Neber, J. N.: Agranulocytosis Following Diamox Therapy, J.A.M.A. **157**:339, 1955.
177. Reisner, E. H., Jr., and Morgan, M. C.: Thrombocytopenia Following Acetazolamide (Diamox) Therapy, J.A.M.A. **160**:206, 1956.
178. Glushien, A. S., and Fisher, E. R.: Renal Lesions of Sulfonamide Type After Treatment With Acetazolamide (Diamox), J.A.M.A. **160**:204, 1956.
179. Gibbs, F. A., Everett, G. M., and Richards, R. K.: Phenurone in Epilepsy, Dis. Nerv. System **10**:47, 1949.
180. Zeifort, M.: Phenurone in Epilepsy, Dis. Nerv. System **10**:245, 1949.
181. Forster, F. M., and Frankel, K.: Fatal Aplastic Anemia During Anti-Convulsant Therapy, Dis. Nerv. System **10**:108, 1949.
182. Lloyd-Smith, D. L.: Phenurone and Hepatitis, Canad. M.A.J. **62**:493, 1950.
183. Levy, R. W., Simons, D. J., and Aronson, S.: Fatal Hepatorenal Syndrome Associated With Phenurone Therapy, New England J. Med. **242**:933, 1950.
184. Simpson, T. W., Wilson, E. B., Jr., and Zimmerman, S. L.: Fatal Aplastic Anemia Occurring During Anticonvulsant Therapy: Probably Idiosyncrasy to Phenurone, Ann. Int. Med. **32**:1224, 1950.
185. Abbott, J. A., and Schwab, R. S.: Serious Side Effects of the Newer Antiepileptic Drugs: Their Control and Prevention, New England J. Med. **242**:943, 1950.
186. Little, S. C., and McBryde, R. R.: The Use of Phenylacetylurea (Phenurone) in Convulsive Disorders, Am. J. M. Sc. **219**:494, 1950.
187. Carter, S., Sciarra, D., and Merritt, H. H.: Phenylacetylurea in the Treatment of Convulsive Seizures, Dis. Nerv. System **11**:139, 1950.

188. Davidson, D. T., Jr., and Lennox, W. G.: Phenacetylurea—Phenurone—in Epilepsy, Dis. Nerv. System **11**:167, 1950.
189. Keith, H. M.: Use of Phenurone in Convulsive Disorders in Children, Am. J. Dis. Child. **80**:719, 1950.
190. Forster, F. M., and Frankel, K.: Insensitivity to Pain as a Complication of Phenurone Therapy in Epilepsy, Dis. Nerv. System **11**:24, 1950.
191. Perry, G. F., and Simonds, S.: Phenacetylurea in Convulsive Disorders, Dis. Nerv. System **12**:200, 1951.
192. Sorel, L., Colle, J., and d'Hollander, L.: Phenylacetylurea in Treatment of Epilepsy, Brit. Abst. A-**111**:1063, 1952.
193. DeJong, R. N.: Phenurone in the Treatment of Psychomotor Attacks, Am. J. Psychiat. **107**:825, 1951.
194. Tyler, M. W., and King, E. J.: Phenacemide in Treatment of Epilepsy, J.A.M.A. **147**:17, 1951.
195. Forster, F. M.: Therapy in Psychomotor Epilepsy, J.A.M.A. **145**:211, 1951.
196. Liversedge, L. A., Yates, P. O., and Lempert, H.: Acute Yellow Atrophy of the Liver Following Treatment With Phenylacetyl-Urea, Lancet **1**:242, 1952.
197. Brandt, S.: Phenylacetylurea in Treatment of Epilepsy, Ugeskr. Laeg. **114**:181, 1952.
198. Bastie, J., and Fernandez, A.: L'électro-choc sous phénacetylurea, Presse méd **60**:471, 1952.
199. Field, J. B., and Justi, R. A.: Fatal Hepatitis After Phenurone Therapy for Epilepsy, New England J. Med. **251**:147, 1954.
200. Della Beffa, A., and Donati, A.: On the Treatment of the Epileptic Syndrome With Phenacetylurea, Ann. Neurol. **59**:1, 1953.
201. Craddock, W. L.: Use of Phenacemide in Epilepsy, With Analysis of Fatal Reactions and Case Report, J.A.M.A. **159**:1437, 1955.
202. Livingston, S., and Kajdi, L.: Use of Phenurone in the Treatment of Epilepsy, J. Pediat. **36**:159, 1950.
203. McQuarrie, I., Anderson, J. A., and Ziegler, M. R.: Observations on the Antagonistic Effects of Posterior Pituitary and Cortico-Adrenal Hormones in the Epileptic Subject, J. Clin. Endocrinol. **2**:406, 1942.
204. Davenport, V. D.: Relation Between Brain and Plasma Electrolytes and Electroshock Seizures Thresholds in Adrenalectomized Rats, Am. J. Physiol. **156**:322, 1949.
205. Woodbury, D. M., and Davenport, V. D.: Brain and Plasma Cations and Experimental Seizures in Normal and Desoxycorticosterone-Treated Rats, Am. J. Physiol. **157**:234, 1949.
206. Gordan, G. S., and Aird, R. B.: Sublingual Desoxycorticosterone for the Control of Convulsive Seizures, Ciba Clinical Symposia **3**:57, 1951.
207. Klein, R., and Livingston, S.: The Effect of Adrencorticotropic Hormone in Epilepsy, J. Pediat. **37**:733, 1950.
208. Hawkes, C. D.: N-Benzyl-B-Chloropropionamide (Hibicon), A New Approach to Anticonvulsant Therapy, Arch. Neurol. & Psychiat. **67**:815, 1952.
209. Kaplan, L. A., and Moslanka, S.: Hibicon—A New Anticonvulsant, Dis. Nerv. System **13**:3, 1952.
210. Livingston, S.: The Use of Hibicon in the Treatment of Epilepsy, J. Pediat. **43**:673, 1953.
211. Tower, D. B.: Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex; An Approach to Its Control in Vitro and in Vivo, Neurology **5**:113, 1955.
212. Stamps, F. W., Gibbs, E. L., and Haase, E.: Epileptic Patients Treated With Aureomycin, Dis. Nerv. System **12**:227, 1951.
213. Perlstein, M. A.: Prenderol: New Drug Used With Retarders in Petit Mal Epilepsy, Neurology **3**:744, 1953.
214. Ellebjerg, J.: Dimedion, New Antiepileptic, Ugesk. f. laeger **111**:1191, 1949.
215. Lund, M.: Dimedion in Treatment of Epilepsy, Ugesk. f. laeger **111**:1195, 1949.
216. Ellebjerg, J., Lung, M., and Saxe, L.: Treatment of Epilepsy With Dimedione, Ugesk. f. laeger **112**:266, 1950.
217. Stamps, F. W., Marshall, W. H., Orloff, M. J., Gibbs, F. A., and Pfeiffer, C. C.: Atrolactamide Treatment of 300 Epileptic Patients, J. Pharmacol. & Exper. Therap. **106**:418, 1952.
218. Molony, C. J., and Parmelee, A. H.: Convulsions in Young Infants as a Result of Pyridoxine (Vitamin B_6) Deficiency, J.A.M.A. **154**:405, 1954.
219. Coursin, D. B.: Convulsive Seizures in Infants With Pyridoxine Deficient Diet, J.A.M.A. **154**:406, 1954.
220. Reilly, R. H., Killam, K. F., Jenney, E. H., Marshall, W. H., Tausig, T., and Apter, N. S.: Convulsant Effects of Isoniazid, J.A.M.A. **152**:1317, 1953.
221. Hunt, Andrew D., Stokes, Joseph, Jr., McCrory, Wallace, and Stroud, H. H.: Pyridoxine Dependency; Report of a Case of Intractable Convulsions in an Infant Controlled by Pyridoxine Pediatrics **13**:140, 1954.

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222. Livingston, S., Hsu, Jeng Mein, and Petersen, D. C.: Ineffectiveness of Pyridoxine (Vitamin B_6) in the Treatment of Epilepsy, Pediatrics **16**:250, 1955.
223. Fox, J. T., and Tullidge, G. M.: Pyridoxine (Vitamin B_6) in Epilepsy, Lancet **2**:345, 1946.
224. Ernsting, W., and Ferwerda, T. P.: Vitamin B_6 in the Treatment of Epilepsy, J.A.M.A. **148**:1540, 1952, (Abst.).
225. Livingston, S., and Sweet, A.: The Use of 3-Methyl-5, Phenyl Hydantoin (AC 114) in the Treatment of Epilepsy. (A Preliminary Report.), Bull. Johns Hopkins Hosp. **86**:359, 1950.
226. Pearson, P. H., Peck, J. L., and Livingston, S.: Fatal Pancytopenia Following Therapy With Nuvarone (3-Methyl-5-Phenyl-Hydantoin). A Case Report, Bull. Johns Hopkins Hosp. **91**:341, 1952.
227. Isaacson, S., Gold, J. A., and Ginsberg, V.: Fatal Aplastic Anemia After Therapy With Nuvarone, J.A.M.A. **160**:1311, 1956.
228. Pryles, C. V., Burnett, J. M., and Livingston, S.: Acute Hepatic Necrosis With Death Occurring During Phethenylate Sodium Therapy. Report of Two Cases, J.A.M.A. **148**:536, 1952.
229. Butscher, W. C., and Gallager, H. S.: Fatal Hepatic Necrosis Occurring During Therapy With Phethenylate Sodium, J.A.M.A. **148**:535, 1950.
230. Kant, F., Warren, E. G., Peters, H. A., and Bowman, H.: Ammonium Chloride as an Adjuvant to Anticonvulsant Medication in Epilepsy, Neurology **3**:336, 1953.
231. Perlstein, M. A.: Use of Meprobamate (Miltown) in Convulsive and Related Disorders J.A.M.A. **161**:1040, 1956.
232. Zimmerman, F. T., and Burgemeister, B. B.: Use of N-Methyl-a-a-Methyl-Phenyl-Succinimide in the Treatment of Psychomotor Epilepsy, Arch. Neurol. & Psychiat. **72**:720, 1954.
233. Zimmerman, F. T.: Milontin and Other New Drugs in the Treatment of Petit Mal Epilepsy, South. Med. J. **47**:929, 1954.
234. Zimmerman, F. T., and Burgemeister, B. B.: Drugs Used in Treatment of Patients With Petit Mal Epilepsy, J.A.M.A. **157**:1194, 1955.
235. Livingston, S., and Pauli, L.: The Use of Celontin (PM 396) in the Treatment of Epilepsy, Pediatrics, In press.
236. Livingston, S.: The Use of Peganone (AC 695) in the Treatment of Epilepsy, J. Pediat. **49**:728, 1956.
237. Bradley, C.: Behavior Disturbances in Epileptic Children, J.A.M.A. **146**:436, 1951.
238. Oettinger, L. Jr.: The Relationship of Epilepsy and Hyperactive Behavior Problems, Epilepsia **2**:148, 1953.
239. Ounsted, C.: The Hyperkinetic Syndrome in Epileptic Children, Lancet **269**:303, 1955.
240. Davidson, Douglas T., Jr., and Lombroso, Cesare: Epilepsy, New England J. Med. **251**:897, 1954.
241. Moore, Matthew T.: The Treatment of the Epileptic Individual, J. Albert Einstein Med. Cent. **3**:12, 1954.

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Special Note

THE RESPONSIBILITIES OF THE MEDICAL PROFESSION IN THE USE OF X-RAYS AND OTHER IONIZING RADIATION

STATEMENT BY THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION

I. INTRODUCTION

1. The United Nations General Assembly, being aware of the problems in public health that are created by the developments of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radiotherapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

2. Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation in the detection, diagnosis, and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable, therefore, to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

II. GENERAL SURVEY OF THE IRRADIATION OF HUMAN BEINGS

3. Man has always been exposed to some irradiation from natural sources. To this has now been added, as a result of modern discoveries and the applications of ionizing radiation and radio activity, certain forms of artifical irradiation.

4. *Natural irradiation* is due to: (1) cosmic radiation; (2) "background" gamma radiation from radioactive substances present locally in the earth, rock or building materials, and from disintegration products of radon in air; (3) radiations emitted from natural radicelements such as potassium 40, radium, radon, and carbon 14 which are incorporated in the body.

5. The amount of this natural radiation varies with locality, but has been estimated as usually delivering between 70 and 170 mrems* per year to the gonads. Of this total, the major contributions are of about 45 per cent from local gamma radiations, 30 per cent from cosmic rays, and 20 per cent from body potassium 40.†

6. *Artificial irradiation* is derived from: (1) the contamination of the environment, the atmosphere, or water by radioactive waste from atomic industries or from users of radicelements; (2) the radioactive fallout, at greater or lesser distances from the source, or radioactivity resulting from the explosion of nuclear devices; (3) the occupational exposure of certain groups of workers, medical practitioners, radiologists, dentists, nurses, atomic energy workers, uranium or thorium miners, and the industrial or scientific users of radiation generators or radioactive isotopes; (4) the medical use of x-ray, other ionizing radiations, and radioelements in the detection, diagnosis, investigation, and treatment of human diseases; (5) the use of certain devices which emit radiation, such as television receivers, watches with luminous dials, and the x-ray generators used for the purpose of fitting shoes.

*Editor's Note: A millirem (mrem) equals approximately 0.001 roentgen.

†From reports sent by India, Sweden, the United Kingdom, and the United States of America.

7. The amount of artificial radiation must vary considerably in different countries and we have inadequate information as to the over-all significance of these factors. In certain countries where estimates have been made, it appears that the greatest gonad irradiation of the population is due to diagnostic radiological procedures, the amount from this source about equalling that from all natural sources in certain instances. The total present contribution from occupational exposure, from the products of atomic industries from radiotherapy, and from the radiating devices mentioned above (paragraph 6, subparagraph 5) is likely to be very considerably smaller; that from radioactive fallout to the gonads appears at present to be in the region of 1 per cent of the natural gonad irradiation in most areas.*

8. Both the magnitude and the significance of these various sources are under review by the Committee. Since medical irradiation accounts for a substantial if not the major proportion of all artificial exposure, it is important that its magnitude should be known accurately for different countries and circumstances. The possibility of making such an assessment depends upon the help of the medical profession, and particularly on the adequacy and availability of records kept by doctors, dentists, and organizations responsible for the use of ionizing radiation.

III. RADIATION HAZARDS

9. The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation and treatment of human disease, but the possible effects of this irradiation on individuals require examination.

10. Generally speaking, the irradiation of living beings may produce radiobiological effects either on the irradiated individual himself or, through him, on his descendants; the former being termed somatic and the latter genetic effects. Somatic effects vary according to the different organs or tissues affected, and range from slight and reversible disturbances such as cutaneous erythema to the induction of leukemia or of other malignant diseases. The possible reversibility of the somatic effects of radiation received in small doses or at low dose rates encourages the belief that there are permissible doses of radiation which will not cause completely irreversible or significant somatic damage. The threshold for occasional somatic damage may, however, prove to be low. In the case of genetic effects, on the other hand, there may be no threshold. These effects increase with a frequency corresponding to the total amount of radiation received by the germinal tissues and, in the great majority of cases, are adverse.

11. Many other factors complicate the interpretation of radiobiologic effects. The differences between whole and partial body radiation, between a single exposure and continuous irradiation, or between the effects of different types of radiation are still imperfectly understood. Biologic differences in the radiosensitivity of various tissues, or of the tissues of people of different age or sex, obviously influence the nature of radiation hazards. It is clear, however, that any radiation of gonads, and any substantial irradiation of other tissues, involve a chance of significant damage which requires assessment.

IV. GENERAL RECOMMENDATIONS REGARDING THE MEDICAL AND OCCUPATIONAL IRRADIATION OF HUMAN BEINGS

12. The Radiologic Profession, through the International Commission on Radiologic Protection,† has undertaken a valuable and responsible duty in defining maximum permissible limits of exposure for the main radiation hazards.

13. The establishment of these maximum permissible levels for those who are occupationally exposed to radiation depends on the view that there are doses which, in the light of our present knowledge, do not cause detectable somatic injury in the individual irradiated, and on the consideration that the number of individuals concerned is small enough for the genetic effects on the

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*According to the reports sent by the United Kingdom and the United States of America.

†See the report of the International Commission on Radiological Protection, published in the *British Journal of Radiology*—Supplement 6. of December, 1954, in the *Journal Français d'électroradiologie*—No. 10, of October, 1955.

whole population to be negligible. For the gonads, or for irradiation of the whole body, the levels are such as to exclude doses greater than 0.3 rem in any week or 3.0 rem in any 13 weeks, or a sustained irradiation rate greater than 5 rem per year. These values imply that no total dose of over 50 rem will have been received by the gonads by the age of 30, or of over 200 rem by the whole body by the age of 60, in any occupationally exposed person.*

As regards irradiation of the whole population, it is considered prudent to limit the average dose to germinal tissues from artificial sources to the order of magnitude of that received from all natural sources.

14. In considering the extent to which the population is irradiated for medical purposes, it is essentially the genetic hazard which is involved although it seems possible that in certain circumstances somatic injury may occur occasionally after low doses of radiation arise. Otherwise, the relevant dose is that indicating the mean gonad irradiation among the population as a whole up to the end of the average reproductive period.

15. The extent of such genetic irradiation from diagnostic procedures has been found to be equal to at least 100 per cent of all natural radiation in two countries,† and that from a third equalled at least 22 per cent of this figure.‡ Even before obtaining more exact values for these and other countries, it is clear that the exposure can be substantial in countries with extensive medical facilities, and that it is essential to consider any ways in which this exposure could be reduced without detriment to the existing or developing value of medical radiology.

16. The Committee is therefore anxious to obtain the help of radiologists in suggesting, through appropriate governmental channels, any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods. In particular it would be valuable to know how much the radiation to the gonads could be reduced (a) by improved design or shielding of equipment, (b) by fuller training of any individuals using radiographic or fluoroscopic equipment, (c) by any local shielding of the gonads that is practicable, especially during abdominal or pelvic examination, (d) by the use of techniques involving radiography rather than fluoroscopy when full information can be obtained by this means, (e) by improvement of administrative arrangements designed to obviate unnecessary repetition of identical examinations of the same subject, (f) by a general study of certain medical conditions such as that of peptic ulcers, to identify the circumstances in which the establishment of a radiological diagnosis has or has not a definite influence upon the treatment or prognosis given.

VI. SUMMARY

1. The Scientific Committee on the Effects of Atomic Radiation established by the United Nations General Assembly accepts the view that the irradiation of human beings, and especially of their germinal tissue, has certain undesirable effects.

2. Information received so far indicates that, in certain countries (Sweden, United Kingdom, United States of America), by far the most important artificial source of such irradiation is the use of radiological methods of diagnosis and that this may be equal in importance to radiation from all natural sources. It is possible that such radiation may be having a significant genetic effect on the population as a whole.

3. The Committee is fully aware of the importance and value of the medical use of radiations but wishes to draw the attention of the medical profession to these facts and to the need for a more accurate estimate of the amount of exposure from this source. The help of the medical profession would be most valuable to make it possible to obtain fuller information on this subject.

4. The Committee would be particularly grateful for information through appropriate governmental channels on ways in which the medical irradiation of the population can be reduced without diminishing the true value of radiology in diagnosis or treatment.

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*See the report of the International Commission on Radiological Protection, published in the *British Journal of Radiology*—Supplement 6, December, 1954, in the *Journal Français d'électro-radiologie*—No. 10, October, 1955.

†Sweden; United States of America.

‡United Kingdom.

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Editorials

ON THE NEWS RELEASE ISSUED BY THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF IONIZING RADIATION

This* is another of several reports or news releases issued in recent months by various committees on the subject of the biologic hazards of ionizing radiation. That radiation has certain undesirable effects can hardly be news to physicians who worked with x-rays at the turn of the century, and who not infrequently suffered unwitting severe radiation damage from excessive radiation exposure. Indeed, memory of these experiences has served to warn most physicians that x-ray examinations should not be undertaken without clearly established reason. It seems unlikely, therefore, that it will be possible to reduce the number of x-ray diagnostic procedures used in medical practice today by further education of the medical profession.

One of the serious omissions of this and similar reports issued recently is the absence of an attempt to equate the dangers of ionizing radiation with the benefits of clinical x-ray exposure. Unfortunately, much of the information on the dangers of ionizing radiation permits one only to speculate on the form which such an equation might take. Until better data on the biologic effects of ionizing radiation are available, any discussion of the relative advantages and disadvantages of diagnostic x-ray examinations must be quite unsatisfactory. However, from the experience of the past 60 years, the negligible amount of radiation damage which has occurred somatically and perhaps even genetically (although sufficient time has not passed to properly assess this factor) is reassuring to all physicians. This reassurance can be further emphasized by the fact that, even before the current flurry of interest in the problems of radiation, many radiologic investigators had begun serious study of methods to reduce radiation exposure substantially below present levels. The next few years should see considerable progress in this direction.

There may be one final note which is worth recording here. As indicated above, a number of committees have been concerned with the problem of radiation hazard in recent years. The problems in the control of ionizing radiation are serious, and there seems little doubt that the increased use of atomic energy in our civilian life will make them more so in a short time. There is a considerable need, therefore, for a top government agency to assume responsibility for

*See Special Note, Page 81, this issue.

such control. Since the United States Public Health Service is charged with the maintainence of the public health of this nation, it seems reasonably clear that the time is at hand when the U. S. P. H. S. should establish within its structure a division or bureau to take charge of these problems. Certainly, we cannot go on much longer dealing with these problems by the committees of scientific and other agencies which have neither the authority nor the responsibility to act effectively.

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ECOLOGY AND CORONARY HEART DISEASE

In a recent and stimulating article, Dr. Alan Gregg has suggested that ecology might well constitute an era in medicine that would equal in importance the eras of logic and experimentation.[1] Ecology is that branch of biology which deals with the mutual relations between organisms and their environment and is frequently used to describe that part of medical science commonly referred to as epidemiology. Ecology has a somewhat broader connotation than epidemiology and may better meet present-day needs in the medical sciences since it strongly demands that attention be given to multiple causation and interaction. Ecology also has a certain advantage in that it provides a strong tie with the social sciences and, in particular, with those branches whose content is primarily the study of the interaction between man and his cultural and physical environment.

Ecologic analysis becomes a tool to provide new knowledge about a particular disease when there can be demonstrated an interaction between host factors and environmental factors which is associated with the occurrence of the disease itself. Only recently has the existence of such relationships been fully appreciated in heart disease. These have been excellently reviewed for coronary heart disease by Miller and his associates.[2]

The probability of productively identifying disease producing interactions between host and environment in a given population is largely dependent upon the availability of facilities to "hold constant" all but a single pair of variables and then to study the partial effects of one upon the other. Variables can be held constant in two ways: either statistically through multiple correlation analysis, or some variant of this technique, or by studying only those population segments where factors needed to be held constant are known not to vary. Occasionally a combination of these procedures has been employed, although for the most part epidemiologic studies have relied heavily upon the latter. This is true primarily because the number of observations needed for detailed statistical analysis is frequently prohibitive, because of inability to measure the variables involved, or because the mathematical techniques needed for such analysis are not clearly understood.

As a general rule, among those items to be held constant are those not involved in the hypotheses under investigation. For example, in studying relationships to coronary heart disease it is obviously desirable to hold constant such factors as differences in diagnostic criteria, definitions of variables with a known relationship to disease such as age, previous illnesses, and concomitant medical conditions, and, possibly, previous effects of medical treatment.

It seems probable that in many respects ideal conditions for ecologic analysis, as a method for enlarging upon our understanding of heart disease, exist within the United States. Medical education and knowledge are uniform to some degree both because of a common language and shared medical literature and because of academic ties in our medical educational system. Communication

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is probably more highly developed in the United States than other parts of the world with a resultant tendency to standardize medical, diagnostic, and care practices. Moreover, we have a common population census, a common disease nomenclature, and a common vital statistics system.

There probably exists also in our population a lack of uniformity in the distribution of heart disease of sufficient magnitude to make ecologic analysis productive as a method for understanding the principles involved in the propagation of this disease. Over 30 years ago, Jessamine Whitney of the American Heart Association reported on geographic differences in heart disease within the United States.[3] For the 40 States then included in the death registration area, she reported annual death rates ranging from 82 per 100,000 population in North Dakota to 273 in Vermont and 262 in the state of New York. Despite sweeping improvements that have taken place in our death registration system since that time, the pattern of deaths from heart disease observed by Miss Whitney has continued to exist. Whereas she attributed higher mortality in certain parts of the country to "thickly settled areas and older populations," it now appears that these factors were probably of minor importance. While no recent data are available, a study of mortality from diseases of the heart conducted by Mary Gover for the year 1940 shows large geographic differences even when rural areas are studied separately and after adjustment is made for differing age distributions in various parts of the country. For rural areas of North Dakota, for example, Miss Gover reported an age-adjusted death rate among white men for diseases of the heart of 226 per 100,000 population as compared with a death rate of 318 and 403 in rural areas of Vermont and New York, respectively.[4]

Of particular interest are geographic differences that exist within the United States in death rates for coronary heart disease. For the year 1950, age-adjusted death rates for white men and women were roughly twice as high in some states as in others.[5] For white men in the age group 45 to 64 the death rate for coronary heart disease varied from 309 per 100,000 population in New Mexico and 374 in North Dakota to 653 in the state of New York. It would not be expected that differences of this magnitude within the United States could be due to different standards of diagnosis, nor do they appear to be. For the age groups in which coronary heart disease is an important cause of death, the geographic differences in these death rates are reflected in differences in the death rates for all causes. For example, among white men in the age group 65 to 74, the death rate for coronary heart disease ranged from 11.6 per 1,000 in the East South Central states (Kentucky, Tennessee, Alabama, and Mississippi) to 19.6 per 1,000 in the Middle Atlantic states (New York, New Jersey, Pennsylvania) while the death rate for all causes varied from 44.6 per 1,000 in the East South Central states to 54.0 in the Middle Atlantic states. Moreover, disease categories which might be confused with coronary heart disease in the assignment of causes of death show no tendency to be negatively correlated with coronary heart disease as might be expected were there great differences in diagnostic standards. Rather, they are positively correlated, or show no correlation at all.

Geographic differences in death rates for all causes within the United States, differences not otherwise explained by age, sex, and race differences among the

states, do not appear to be due to the migration of sick populations—those populations for which the risk of dying is great. Some estimate of the migratory habits of these populations can be obtained by studying the data on residence reallocation of death certificates among the states.[6] Under the reallocation procedures, death certificates for persons living in a state for less than one year, or who are in an institution at the time of death, are sent to the state in which the person previously lived. In 1950, 3 per cent of all deaths occurred in some state other than the state of "usual residence." Obviously, individual states both "import" deaths and "export" deaths. The balance between imports and exports would appear to be an estimate of the extent to which death rates might be biased upward or downward due to the migratory habits of populations for which the risk of death is great—biases that remain even after residence correction under the current residence reallocation procedures. In general, states with high death rates tend to export more deaths than they import. In 1950, the Middle Atlantic states, where generally high death rates prevail, exported 3,644 deaths outside of that geographic division while importing only 2,252. On the other hand, the West North Central states, a low death rate area, exported only 2,494 deaths and imported 3,284. Thus, it would appear that the migratory habits of that segment of the population about to die may actually minimize geographic differences in death rates for all causes. If these observations can be projected to deaths from coronary heart disease, we can conservatively estimate that there exist, within the United States, geographic differences in the risk of dying from coronary heart disease of considerable magnitude—differences which are indigenous to each area. Disease producing host and environmental interactions in various parts of the country may vary even more widely, therefore, than a study of available mortality statistics would suggest.

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There exists considerable evidence of the necessary heterogeneity in environmental factors within the United States needed for productive ecologic analysis. Many of the current theories about factors implicated in the etiology of coronary heart disease are theories about our culture—an environmental factor. Much evidence is at hand regarding the presence of diverse cultural groups within our social system.. The great waves of migrations starting with the English migrations in the seventeenth century and culminating in the Puerto Rican migration since Would War II, provide us with culturally (and genetically) different kinds of people within the United States. Despite the fact that the greatest wave of migration occurred during the latter part of the last century, there still remain in our population roughly 10 million foreign-born whites in addition to foreign-born of other races. These persons have, for the most part, now reached the age group where a high incidence of coronary heart disease is observable. Moreover, many of these were born in countries where the risk of dying from coronary heart disease is believed to be much less than the risk in those areas of the United States where these persons have settled.

Evidence also is at hand as to heterogeneity in host factors within the United States. Draft records from World War I reveal that men from various parts of the country differed considerably in their physical measurements, with relatively short men coming from the Northeast and tall lank men coming from the South.[7]

These data on regional distinctiveness along with other evidence have recently been summarized by Dr. Clyde Kluckhohn.[8] There is, in fact, an interesting relationship between the heights of men drafted from each state in World War I and the death rates for coronary heart disease experienced by men in these states in the age group 45 to 64 during the years 1949-1951, with states having the shorter men experiencing higher death rates than states having taller men.[9]

It must be pointed out that there is some artificiality in labeling factors as purely host or environmental, although this is admittedly desirable from a conceptual standpoint. In the association between stature and coronary heart disease mentioned above, for example, the stature of men in the United States has undoubtedly been determined environmentally as well as genetically. Stature is, then, the result of mutual relations between man and his environment; and, if stature were a predictor of coronary heart disease, a study of these mutual relations would be necessary if the pathogenesis of coronary heart disease were to be completely understood.

From the evidence it would appear that ecologic analysis within the United States as a means of increasing the scope of the medical knowledge about coronary heart disease might represent the kind of future in medicine referred to by Dr. Gregg. It would, of course, be important as a first step to verify and to describe more completely geographic differences that exist in coronary heart disease within the United States. Such a verification might incorporate intensive studies of host and environmental relations in various population segments.

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REFERENCES

1. Gregg, A.: The Future Health Officers Responsibility: Past, Present, and Future. Am. J. Pub. Health **46:** 1956.
2. Miller, D. C., Stare, F., White, P. D., and Gordon, J. E.: The Community Problem in Coronary Heart Disease: A Challenge for Epidemiological Research, Am. J. Med. Sc. **232:**329, 1956.
3. Whitney, J. S.: Heart Disease Mortality Statistics, American Heart Association, May, 1927.
4. Gover, M.: Mortality From Heart Disease (All Forms) Related to Geographic Section and Size of City, Pub. Health Rep. **64:**439, 1949.
5. Enterline, P. E., and Stewart, W. H.: Geographic Patterns in Deaths From Coronary Heart Disease, Pub. Health Rep. **71:**849. 1956.
6. U. S. National Office of Vital Statistics. Vital Statistics of the United States, Vol. III, Table 43, 1950. U. S. Government Printing Office.
7. Davenport, C. B., and Love, A. G.: Army Anthropology. Washington, 1921, U. S. Government Printing Office.
8. Kluckhohn, C. Physical Anthropology, Am. Anthrop. **57:**1280, 1955.
9. Enterline, P. E. Factors Associated With Geographic Differences in Coronary Heart Disease, Circulation **14:**5, 1956 (Abstr.).

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Book Reviews

CIBA FOUNDATION COLLOQUIA ON AGEING. VOLUME 2. AGEING IN TRANSIENT TISSUES. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Pp. 263; with 96 figures; indexed. Boston, 1956, Little, Brown and Company. Price $6.75.

Aging is a process which is common to all living organisms. It is characterized by changes which occur progressively with the passage of time. These changes may be observed within the total organism or with respect to specific cells or tissues. Since a number of tissues go through a cycle of growth and decline within the life span of the total animal, they offer unique potentialities for the study of aging. The present volume addresses itself primarily to the changes in these specialized tissues, such as the ovary, the corpus luteum, the placenta, and the red blood cells. Definitive chapters are presented on these topics by competent investigators, with summaries of the pertinent discussion elicited in the symposium. Substantive data on fetal growth and development, organ culture studies, placental function, life span of red cells, and the effects of endocrines on development are presented. Much of the material is orientated toward functional processes in cells and tissues of increasing age.

Within the various chapters, the word aging is used in a variety of connotations. In the final discussion, some resemblance to order came from the suggestion that the word aging be used to denote chronological changes; senescence, an age change associated with reversed growth or systematic reduction in function and growth, an age change associated with progressive increase in tissue or function. The symposium emphasizes the fact that the phenomena of aging show important species differences and questions the assumption that there is a single basic "aging process" that is common to all living organisms.

Although no single unifying conception can be stated which will account for all the observations reported, the data emphasize the importance of environmental factors (hormones, nutrition, etc.) in determining the changes in cellular structure and function which occur with the passage of time. Until these factors can be identified and controlled experimentally, it will be impossible to attribute changes in transient tissues to intracellular mechanisms alone.

Although a large proportion of the symposium was devoted to experimental embryology and endocrine influences on development, consideration of these factors may offer leads for the experimental approach to the basic problem of aging; namely, why and how do individual cells lose their capacity for self-maintenance?

The volume is a valuable contribution to basic biology.

N. W. Shock

A MANUAL OF COMMON CONTAGIOUS DISEASES. By Philip Moen Stimson, A.B., M.D. and Horace Louis Hodes, A.B., M.D. Ed. 5. Pp. 624. Philadelphia, 1956, Lea & Febiger. Price $8.50.

This book contains much useful clinical information. The sections on the specific contagious diseases are lucid, factual, and usually indicative of the authors' wide experience with these infections. The importance of vaccination against smallpox is without question, as also is the need to be prepared to make an appropriate diagnosis of this disease. However, smallpox cannot be considered a *common* contagious disease in the United States or Europe. To exclude from discussion common contagions like "common cold" and influenza seems paradoxical. Perhaps it would be more appropriate to have titled the book without using the word "common."

The introductory chapter could have been excluded without detracting from the book. The general discussion of "infection" and "immunity" is often inaccurate, excessively vague or misleading, and would probably be improved by amplification or exclusion.

The chapter on "Selection of an Antibiotic" seems exceptionally well presented and is very much to the point. However, accumulating data might question the validity of certain statements

such as, "Sulfonamides remain the drug of choice for infections due to meningococci, including septicemia and meningitis."

The last chapter is valuable in describing problems of isolation, quarantine, aseptic techniques, and "General Management of Contagious Diseases." The data presented are not available in such a concise and assimilable fashion from any other source.

Leighton E. Cluff

CARE OF THE LONG-TERM PATIENT. CHRONIC ILLNESS IN THE UNITED STATES. Vol. II. Commission on Chronic Illness. Pp. 606; indexed. Cambridge, 1956. Published for the Commonwealth Fund by Harvard University Press. Price $8.50.

This valuable contribution to the literature of public health and medical care administration is the first of the series of four volumes to be issued by the Commission on Chronic Illness. Volume I, *Prevention of Chronic Illness*, is in press, while Volume III, *Chronic Illness in a Rural Area*, and Volume IV, *Chronic Illness in a Large City*, are expected to be released later this year.

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The Commission on Chronic Illness was created in 1949, by the American Hospital Association, the American Medical Association, the American Public Health Association, and the American Public Welfare Association as an independent voluntary body to study and report on the chronic illness problem. The membership of the Commission was broadly based, including not only professional workers in the health and welfare fields, but also representatives of commercial enterprise, farm and labor organizations, and the general public.

Care of the Long-Term Patient has been largely developed around information assembled for, and conclusions reached at, the National Conference on Care of the Long-Term Patient, which brought together more than 500 persons for three days of intensive work in March, 1954. It includes 443 pages of text plus 163 pages of appendices and index. The first four chapters define and describe the long-term patient and his care and rehabilitation, or lack thereof, at home and in institutions. There follow chapters on personnel and educational needs and resources, on the problem of coordination of services, on research needs, and on financing. The summary chapter brings together the 80 conclusions and recommendations already stated in the eight preceding chapters.

As a comprehensive presentation of the problems of care of the long-term patient, and of various approaches to more adequate care, this volume will be a useful handbook for individuals and agencies working in this field. No doubt its value will be enhanced by the forthcoming publication of Volume I which may be expected, in its discussion of the prevention of chronic illness, to provide further background on the natural history of the more important chronic diseases and the services required for their control.

Perhaps the most valuable aspect of the book is that it stimulates the reader to look at the various phases of the subject from a broad point of view. For example, emphasis is placed on the desirability of handling long-term illness as an integral part of general medical care; the unity of prevention, definitive treatment, and rehabilitation as phases of the over-all needs of the patient is pointed out; and an entire chapter is devoted to the need for, and possible methods of, coordination of services at the local level. Cost of programs, it is stated, should be measured first in terms of human values; it is good economy to restore the individual quickly to productive health. It is recommended that programs be planned around the needs of all long-term patients rather than for special segments of the population. With regard to personnel problems, it is stressed that not only are more technically trained people needed, but also that these workers need special orientation regarding the needs of long-term patients to develop and maintain their interest in working with this group.

In view of the many agencies, public and private, concerned with long-term care, a full chapter on "coordination and integration" is well warranted. The Commission found a variety of ways in which state and local health departments have conducted demonstrations and studies, notably in New York, New Jersey, Maryland, Virginia, and California. Undoubtedly, these will serve as examples for other communities. With the great diminution in communicable diseases,

and with the increasing percentage of older persons in our population, emphasis in health departments must shift to include chronic conditions. And in this field, prevention and care are closely interwoven.

The recommendations on financing recognize the "gaps, overlaps, and imbalance that now characterize the financing of much long-term care," and call for increased funds from present sources, such as voluntary insurance, workmen's compensation, industrial and union plans, and public agencies. It is pointed out that not only are more funds needed, but also improved ways of using them. The chapters on coordination and on research for planning and administration suggest approaches toward more effective use of funds.

The book makes effective use of brief case histories to illustrate both problems and methods for their solution. The detailed tables of contents at the beginning of each chapter and the comprehensive index add substantially to the utility of the volume. The listing of the names and titles of the participants in the 1954 Conference, and the data contained in the appendices provide useful reference material.

It is a tribute to the broad gauge membership of the Commission that 34 individuals of varied backgrounds found such agreement that a minority report was submitted on only one point, namely the desirability of extension of Social Security benefits to the totally and permanently disabled. It is of interest to note that while the book was in press the Congress, in enacting the 1956 amendments to the Social Security Act, in effect adopted the recommendation of the 13 minority members of the Commission on this point.

Care of the Long-Term Patient is a valuable stimulant to thought on a timely subject and should be in the library of every health and welfare worker concerned with chronic illness.

Otis L. Anderson

PRINCIPLES OF CLINICAL ELECTROCARDIOGRAPHY. By Mervin J. Goldman, M.D. Pp. 310, with several hundred figures; indexed. Los Altos, California, 1956, Lange Medical Publications. Price $4.50.

This is intended as an elementary text for the beginner. It is carefully prepared and produced, economically lithographed in typewriter offset, and is a welcome companion volume to the other useful Lange publications. In general the subject is adequately covered and the illustrations—such an important feature of any text on electrocardiography—are excellently selected and reproduced. The text for the most part is clear and factual. This is not to say, however, that there is no room for criticism; indeed there are numerous minor and a few major defects to which attention should be drawn.

Important as skilful diagrams are, they can be overdone; in the introductory chapters one feels that they are unnecessarily plentiful and that their very superabundance leads to confusion. On page 74 one is surprised to find a frankly inverted T wave in Lead I regarded as normal without adequate extenuating explanation.

The para-arrhythmias are ill treated. Complex as they are, they especially deserve clear and accurate presentation. Unfortunately the uninitiated reader will be left confused and misinformed. The definition of parasystole is inaccurate (or at best misleading) and, when one turns the page to interference-dissociation, there is worse to come. This form of A-V dissociation is stated to be "a complete A-V heart block"; and again, "the etiology, clinical significance, prognosis and treatment are the same as for complete heart block." This, of course, is palpable nonsense. The essence of interference-dissociation is that forward A-V conduction is not only possible but often normal—otherwise there could be no "interference" or "capture" beats.

A feature of the book is a final chapter comprising a series of about 60 tracings for interpretation. These are a good selection but disappointment is keen when it is soon realized that they are but a resurrection of tracings previously used throughout the text, now reassembled for a final parade.

A handful of references are appended at the end of the text, but these are ill assorted. Two of the four books and four of the six articles listed also emanate from California (from Prinz-

metal's laboratory). In fact the total of three sources included may be summarized as Prinzmetal, Lepeschkin, and Scherf—mighty names in the field to be sure, but certainly not the only ones to be quoted, if a useful and balanced bibliography is to be included.

In summary, the diligent reader of these pages cannot help but acquire a reasonable working knowledge of electrocardiography; on the other hand, however, the text is not without serious blemish and appears to possess no outstanding virtue that would single it out for special recommendation to the beginner.

Henry J. L. Marriott

Announcements

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Applications are now being accepted for the second course in the Training Program for Steroid Biochemistry to start October 1, 1957. The program is conducted through the cooperative effort of the Worcester Foundation for Experimental Biology, with the Department of Chemistry, Clark University, at Worcester, Massachusetts, and the Department of Biochemistry, College of Medicine, University of Utah, at Salt Lake City, Utah.

The training program is sponsored by the National Cancer Institute of the National Institutes of Health, U.S.P.H., to provide specialized training for individuals interested in steroid investigation. Two groups of candidates will be selected and will receive stipends during the period of training.

Postdoctoral candidates having an M.D. or Ph.D. degree will receive $5,000 for one year starting October 1, 1957. The training will consist of laboratory and lectures covering theoretical and practical aspects of steroid research and an opportunity to engage in a research problem under an established investigator.

Candidates having a B.S., M.S., or equivalent degree will receive $1,500 for a six months' training period, October 1, 1957, through March, 1958. The predoctoral program is intended to provide competency in the analysis of steroid compounds for research and clinical laboratories.

The closing date for applications will be August 15, 1957. Requests for applications should be made to Dr. Kristen Eik-Nes, Department of Biochemistry, College of Medicine, University of Utah, Salt Lake City, Utah, or to Dr. Frank Ungar, Department of Chemistry, Clark University, Worcester, Massachusetts.

AVAILABILITY OF SYMPOSIUM NUMBERS

Since the first publication of this JOURNAL in January, 1955, several entire issues have been devoted to Symposium numbers on topics of major interest. These Symposia are usually complete discussions, which cover conflicting points of view if necessary, which often include some original work of the several authors as well as up-to-date presentation of the literature (more current than is obtainable even in recently published textbooks), and which in general may be expected to remain scientifically valid for two or more years. The Symposia are of especial value to teachers and to medical students, as well as to practitioners.

Those so far published, with dates of publication, Guest Editors, and Symposium title, are listed here.

May, 1955	(Guest Editor, David Seegal): The Management of Patients with Primary (Essential) Hypertension. (Out of stock.)
October, 1955	(Guest Editors, Lester Breslow and Dean W. Roberts): Screening for Asymptomatic Disease. (Of special interest to public health officers and to hospital clinics.) (26 issues in stock.)
July, 1956	(Guest Editor, Louis Lasagna): Pain and Its Relief. (210 issues in stock.)
October, 1956	(Guest Editor, Robert L. Levy): Coronary Heart Disease. (45 issues in stock.)
January, 1957	(Guest Editors, David P. Earle and David Seegal): Glomerulonephritis. (105 issues in stock.)
April-May, 1957	(Guest Editor, David T. Smith): Chronic Fungus Infections. (246 issues in stock.)
June, 1957	(Guest Editor, Joseph J. Bunim): Rheumatoid Arthritis. (Published June 3.)

These several Symposium numbers, together with others to appear in future issues, may be separately purchased at $2.00 per single copy (while the supply lasts). Orders should be sent directly to the publisher, The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Missouri.

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